No. 13,259

IN THE

United States Court of Appeals

FOR THE NINTH CIRCUIT

WOODARD LABORATORIES, INC., DEAN D. MURPHY and JOHN L. SULLIVAN,

Appellants,

vs.

UNITED STATES OF AMERICA,

Appellee.

BRIEF OF APPELLANTS.

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I.
STATEMENT OF JURISDICTION.

This is an appeal from judgments of conviction imposed against Appellants following a trial by court after a jury had been waived upon an Information charging them in ten counts with violation of the Federal Food, Drug and Cosmetic Act. [R. 28, 29 and 3.] Appellants will through this Brief be referred to as defendants. The District Court had jurisdiction under 18 U. S. C., Section 3231 and Rule 18 of the Federal Rules of Criminal Procedure, and 21 U. S. C., Section 333(a) over the offenses charged in the Information and this Court has jurisdiction under 28 U. S. C., Section 1291 to review the decision of the District Court.

II.
STATEMENT OF THE CASE.

In Count I defendants were charged with having shipped on August 22, 1949 in interstate commerce from Los Angeles to Denver a number of boxes of alpha estradiol tablets bearing the trade name "Estrocrine" and labeled that each tablet contained 0.022 milligrams or 22 micrograms of alpha estradiol and that at the time of introduction into interstate commerce said drug was adulterated within the meaning of 21 U. S. C., Section 351(c) in that each tablet did not contain the quantity of alpha estradiol represented on the label.

Count II involved the same set of facts but charged misbranding within the meaning of 21 U. S. C., Section 352(a).

Count III charged that between January 20, 1950 and January 24, 1950 defendants introduced into interstate commerce from Los Angeles to Denver the same product and that it was adulterated for the same reasons set forth in Count I.

Count IV involved the same set of facts alleged in Count III but charged a misbranding within the meaning of 21 U. S. C., Section 352(a) by reason of those facts.

Count V charged that defendants shipped between March 20, 1950 and April 13, 1950 the same product from Los Angeles to Denver and that it was adulterated for the same reasons set forth in Count I.

Count VI involved the same set of facts as those in Count V and alleged a misbranding by reason thereof within the meaning of 21 U. S. C., Section 352(a).

Count VII charged that the defendants on July 12, 1949 shipped from Los Angeles to Texas the same product

and that it was adulterated for the same reasons mentioned in Count I.

Count VIII involved the same set of facts as those alleged in Count VII and charged a misbranding by reason thereof within the meaning of 21 U. S. C., Section 352(a).

Count IX charged that between May 15, 1950 and May 25, 1950 defendants shipped from Los Angeles to Colorado the same product adulterated for the same reasons set forth in Count I.

Count X involved the same set of facts as contained in Count IX and alleged a misbranding by reason thereof within the meaning of 21 U. S. C., Section 352(a).

The Information was filed May 8, 1951. [R. 3 to 31.]

Due to the lengthy nature of the testimony, we have placed in the Appendix the detailed Statement of Facts necessary to a proper determination of this appeal with appropriate references to the record. In this Brief we therefore condense those facts, employing for easy reference the same headings appearing in the Appendix and with appropriate references to the pages of the Appendix. Preliminarily, however, there are a ~~new~~ few matters that should be covered before we commence discussion of the facts.

Defendant Murphy is President of Woodard Laboratories, a corporation [R. 22] and defendant Sullivan is General Manager. [R. 67.] Jury trial was waived by all defendants. [R. 22-24.] The trial of this case commenced in the morning of November 7, 1951 [R. 35] and was concluded late in the afternoon of November 8, 1951. [R. 27.]

The Court found each defendant guilty as to Counts I, III, V, VII and IX and not guilty as to the remaining counts which involved the same set of facts, respectively, as those upon which they were found guilty. Having been found guilty on the adulteration counts, the Court was not empowered to convict them upon the misbranding counts involving the same set of facts. (*United States v. Noble* (C. A. 3rd, 1946), 155 F. 2d 315, 318; *Gebhart v. United States* (C. A. 8th, 1947), 163 F. 2d 962.)

The sentences imposed upon the defendants were as follows: Against Murphy and Sullivan each $50.00 on each of Counts I, III, V, VII and IX, or a total fine of $250.00 each. Against Woodard Laboratories, Inc., a corporation, $500.00 on each of said Counts, or a total fine of $2500.00. [R. 28 to 32.] We are informed that the fine against Woodard is the largest imposed under the Food and Drug Act during 1951 against any defendant.

Notice of Appeal was served and filed by each of the defendants. [R. 32, 33.]

Though the name of the drug involved is "alpha-estradiol," it is also frequently referred to as "estradiol." For purposes of convenience, it will hereinafter be referred to as "estradiol." Likewise the word "milligrams" will be abbreviated as mg. and "micrograms" as mcg. also instead of using the full corporate name of Woodard Laboratories, Inc., the corporation will hereinafter be referred to as "Woodard."

Because of its importance in this proceeding, we also include in the Appendix (App. 52) an exact copy of the monograph for alpha-estradiol tablets appearing on page

227
~~277~~ of the Fourteenth Revision of the United States Pharmacopaeia referred to in this Brief as U. S. P. XIV.

Motion for judgment of acquittal was made at the close of the Government's case and the defendants' case [R. 85, 280] though not necessary to raise the question of the sufficiency of the evidence on appeal in view of Rule 52(a), Federal Rules of Criminal Procedure. (*United States v. Renee Ice Cream Co.* (C. C. A. 3rd, 1947), ~~165~~ 160 F. 2d 353, 355.) The trial court attached no importance to the motion because a jury was not impaneled. [R. 84, 85.]

III.
CONDENSED STATEMENT OF FACTS.

(1) The Manufacture and Shipment of the Products Involved.

These products were manufactured by Crest Laboratories of Burbank and the completed products furnished to Woodard, who packaged and shipped them. The estradiol used in the manufacture was delivered to Crest upon order from Woodard by International Hormones of Brooklyn, New York. The orders placed by Woodard with Crest were for quantities of 22 mcg. tablets and 110 mcg. tablets. (App. 1.)

The manufacturing methods employed by Crest Laboratories were according to the standard accepted methods in the pharmaceutical manufacturing field. Lot numbers for purposes of identification were assigned by Woodard to each of the quantities received by them in turn from Crest. The products involved in Counts I, II, VII and VIII bore Woodard Lot No. 497,567. At the time that these were manufactured a work sheet was prepared by Crest and assigned Control No. 2571 and was recevied

in evidence as Exhibit "B." A work sheet was also prepared by Crest for the manufacture of the 110 mcg. tablets manufactured at the same time and assigned Crest Control No. 2570. This work sheet was received in evidence as Exhibit "E." The products involved in Counts III and IV bore Woodard Lot No. 897,618. A work sheet was prepared by Crest for these and assigned Control No. 2800 and this work sheet received in evidence as Exhibit "C." The 110 mcg. tablets manufactured at the same time were assigned Control No. 2803 and the work sheet therefor received in evidence as Exhibit "F." The products involved in Counts VI, VII, IX and X bore Woodard Lot No. 107,694. A work sheet for the manufacture of the 22 mcg. tablets subject of those counts was prepared by Crest and assigned Control No. 3180 and the work sheet received in evidence as Exhibit "D." The 110 mcg. tablets manufactured at the same time were assigned Control No. 3181 by Crest and the work sheet for that batch received in evidence as Exhibit "G."

The 22 and 110 mcg. tablets were manufactured in precisely the same way with the same ingredients and correspondingly the same amounts thereof except of course the quantity of estradiol in the 110 mcg. product was greater than in the 22. (App. 2, 3, 4, 5.)

In the manufacture of all of these products an overage of 5% more estradiol was used than necessary to finish a completed product each containing 22 or 110 mcg. of estradiol as the case may be. (App. 5, 6.)

The manufacturing process was described in detail and involved a series of steps commencing with weighing of the individual ingredients by the supply department, again weighing when received in the manufacture, the mixing

of all of these ingredients in a pharmaceutical mixing machine, together with the estradiol, so that as mixed the entire mass was one homogeneous wet mass. The extrusion of this mix then through another machine, the particles of the mix then extruded resembling macaroni, the granulating of this mass, drying it, and finally its compression into tablets in the tableting machine. (App. 6, 7.)

Upon completion these products were shipped to Woodard, who packaged and shipped them on the dates and to the persons specified in Exhibit 1.

(2) Assays of Samples of the Product Are Made by the F. D. A. and the Results Thereof.

As shown by Exhibit 1, the Stipulation of Facts, samples of the products in each count were picked up and delivered to Jonas Carol of the Food and Drug Administration for laboratory analysis and assay. All of these assays occurred either in the latter part of 1949 or the early part of or up to the middle of 1950. (App. 8-15.) [Ex. 1.]

Two witnesses for the Government testified, both employees of the Food and Drug Administration and men of unquestioned competence. Their testimony amounted to this: that the samples in question were analyzed by them, some according to the U. S. P. procedure and some with deviations therefrom and that the amount of estradiol recovered ranged from approximately 6 to 16 mcgs., depending upon the particular sample assayed. The U. S. P. assay procedure contemplates first a series of four extractions in the method described in U. S. P., the purpose being to extract the estradiol present in the material and then after extraction by use of a colorimeter to estimate the quantity of estradiol actually extracted. We have

attached in the Appendix to this Brief a copy of the monograph for estradiol, or alpha estradiol, tablets appearing in U. S. P. XIV at page 227, which shows the steps to be taken in the assay procedure. (App. 52.)

Following the assays mentioned these men conducted four additional extractions of the samples and did not extract any more estradiol.

Following that they attempted to simulate the tablets in question by using quantities of excipients or materials which they considered were commonly used in tablets of this sort. They did not, however, use all of the excipients present in the Woodard tablets and in one respect used an excipient which was not present in the tablet. Also these excipients were allowed to remain in powdered form and were at no time put through the manufacturing process employed in making the Woodard tablets, nor was the mixture ever compressed into tablet form. The U. S. P. method of assay provides that a tablet containing 22 mcgs. of estradiol shall be used. Therefore if a tablet was represented, such as the Woodard tablets, to contain 22 mcgs., it would be necessary to take 10 tablets for the purpose of assay. Thus in conducting this simulated experiment these men took the equivalent of 9 or 10 of such tablets in powdered form and added 200 mcgs. of estradiol. The U. S. P. assay was run and approximately 97% of the amount of estradiol put into this experimental mixture was recovered. (App. 10-16.)

The witnesses for the Government and the witnesses for the defense (all of whom were experts) were all in agreement up to a certain point; that in assays conducted by them of samples of the Woodard tablets, they were unable to recover the labeled potency of 22 mcgs. The

reasons for this lack of recovery was where the point of difference existed, the inference being from the testimony of the Government witnesses that by reason of their assay results no more estradiol was in these tablets at the time of shipment than they recovered in their assay. The testimony of the defense witnesses on the other hand was that the U. S. P. method of assay is wholly unsuitable and inaccurate for the assay or determination of the infinitesimal amount of estradiol in a tablet such as the Woodard 22 mcg. tablets, and an experiment was conducted by expert witnesses for the defense to prove that to be the case. That, however, will be dealt with shortly in this discussion of the facts.

(3) An Official Assay Method Is Adopted After the Manufacture and Shipment of the Products in Question.

No official assay method for estradiol tablets existed prior to the date that the fourteenth revision of U. S. P. became official on November 1, 1950. That method appeared on page 227 of that work. (App. 16, 18, 52.) All of the products in question here were shipped prior to November 1, 1950; one shipment was on August 22, 1949, another January 24, 1950, another April 13, 1950, another July 12, 1949 and the last May 25, 1950. [See Ex. 1.] Also all of the assays of these samples conducted by the Government witnesses were made prior to the time that the U. S. P. method became official and in some cases before it was known that it would be listed and recognized in U. S. P., or in fact that any method of assay existed. [Ex. 1.] (App. 16, 18, 22, 25, 31.) The Government witnesses, however, were able to follow the procedure that subsequently appeared in U. S. P. be-

cause they had participated in the formulation of the assay method itself and of course knew it long before its appearance. (App. 9, 13, 14.)

(4) The Notices of Alleged Violations to Defendants.

In the early part of 1950 a Notice of Hearing was received by Woodard from the Food and Drug Administration alleging that samples of the products which subsequently became subject of this litigation had been picked up and upon assay shown to be below the labeled potency of 22 mcgs. A hearing was had before the Administration and a couple of months later another hearing having to do with samples of another shipment, which also became subject of the litigation, was had. Following these hearings Woodard contacted the most competent laboratories in Los Angeles, submitting samples of the products picked up by the Administration for assay and obtained a wide variety of results. Correspondence passed between Woodard and the Administration on the subject and Woodard advised the Administration by a letter dated July 17, 1950 [Ex. 2] of the results obtained by these laboratories and stating that the question had therefore been raised whether any method of assay was suitable for the assay of these particular tablets and accurate results obtained. (App. 19, 20.)

(5) Assays of Samples of the Products Are Obtained by Defendants and the Results Thereof.

One of the laboratories retained by defendants was Adam Laboratories of New York. The results of these assays appear in a letter dated December 7, 1950, which is a part of Exhibit 1. This laboratory found the samples assayed to be equal to the labeled potency. Consequently

the deposition of Elizabeth Adam Weiss, the head of this laboratory, was taken in New York City by counsel for defendants in July, 1951. Upon returning to Los Angeles and investigating the matter further counsel for defendants was convinced that her assay results were inaccurate, that the assay results obtained by the laboratories in Los Angeles were true and that the opinion of these laboratories that the U. S. P. method of assay was inaccurate and unsuitable for the assay of these low potency products was the true state of facts. It may not properly be part of a statement of facts to make the following observation but we may do so in order that no wrong impression be obtained: In arriving at this conclusion it was not that counsel or the defendants doubted that the labeled amount of estradiol—22 mcgs.—was actually in the tablets at the time of shipment but rather that it would be impossible for Miss Adam, by following the U. S. P. procedure, to *recover* the labeled potency of 22 mcgs. [R. 97, 302, 303.]

The other laboratories retained by defendants were Shankman Laboratories, Bio-Science Laboratories and Truesdail Laboratories. The results of their assays of samples of the Woodard tablets ranged from 9.1 mcgs. per tablet to 14½. (App. 19, 21.)

Their testimony, with the exception of Truesdail Laboratories, through Dr. Jeffreys, was not offered for the obvious reason that it would all be cumulative and simply establish but one thing, that no more than 14½ mcgs. per tablet of estradiol could be recovered from tablets with the excipient present actually containing 22 mcgs. under the U. S. P. method of assay. (App. 21.)

Dr. C. E. P. Jeffreys, Technical Director of Truesdail Laboratories, one of the largest and most widely known laboratories in Southern California, holds a Ph.D. degree in Chemistry from the California Institute of Technology and possesses the other qualifications appearing in the record. (App. 21.) Prior to July 27, 1950, he had been requested by Crest Laboratories to assay a sample of one of these tablets of the 22 mcg. potency. He refused to do so, however, because at the time there was no acceptable method known for commercial assay of such a low estradiol potency product. About July 27, 1950, however, he received a copy of what was to become U. S. P. XIV. At about that time he was requested by Woodard to run an assay of a sample of one of the Woodard tablets in question and he did so strictly according to the U. S. P. method. Following that method precisely the recovery of estradiol was so low that he felt the difficulty was in lack of complete extraction of the infinitesimal amount of estradiol present in combination with the large mass of excipients (this ratio actually was 22 parts estradiol to 324,000 parts excipients) and in order to obtain better results he used a different grinder or mixer for the grinding up of the tablets than the U. S. P. provided. Even with that procedure he was unable to recover more than 9.5 and 9.1 mcgs. per tablet and he could not duplicate results in several assays attempted. (Government witness Carol conceded that when duplication of results could not be obtained the assay procedure is faulty, other things being equal.) (App. 17.) He explained in detail that organic substances such as estradiol adsorbed to the solid surfaces of excipients and that the extraction of the estradiol from those excipients presents a major problem in the science of analytical chemistry.

(App. 23-26.) He pointed out that a microgram was but one-millionth of a gram and in his opinion all of the estradiol was not extracted because of adsorption such as he mentioned. (App. 21, 22, 24.)

The U. S. P. method he said was a very sensitive and cumbersome method and it was also possible under that method for material to be extracted along with the estradiol which would render the final results inaccurate and, too, it would not be possible to know how much estradiol had been adsorbed by or on the excipients. (App. 25.) We refer the Court to the portion of the Appendix in which Dr. Jeffreys' testimony appears in this connection in detail. (App. 21-28.) We simply hit the highlights of it here for the purpose of bringing before the Court the broad picture of the position his testimony discloses.

Another defense witness was Don C. Atkins, presently working on his doctor's degree at U. S. C. in Chemistry. He was director of laboratories at Crest but was not employed by them at the time these tablets were manufactured. He has conducted approximately 100 assays of estradiol tablets and used a colorimeter for the purpose of finally estimating the quantity of material at the end of an assay over 1,000 times. He testified extensively concerning experiments made by him with the U. S. P. procedure for tablets containing 22 mcgs. of estradiol and he stated that no satisfactory results had been obtained and that the presence of the excipients in the tablet rendered the U. S. P. method inaccurate and unsuitable. (App. 29-37.)

He, as well as Dr. Jeffreys, confirmed the fact that prior to the appearance of the U. S. P. method of assay no method of assay had appeared in the scientific litera-

ture for the assay of tablets containing estradiol in combination with other excipients. This is the substance of his testimony and for a more detailed review of it we refer the Court to that portion of the Appendix in which it appears. (App. 31, 29-37.)

(6) Experimental Assays Are Instructed to Be Made by Defendants and the Results.

At the request of counsel for defendants Crest Laboratories, on June 27, 1951, prepared a work sheet for the manufacture of 7,000 tablets each to contain 22 mcgs. of estradiol. This work sheet was given a control number, No. 2571-B, and was received in evidence as Exhibit "H." It was made identically with the work sheets prepared at the time the products in question were manufactured [Exs. B, C and D], using the same excipients, the same amount of estradiol and the same corresponding quantities. (App. 38, 39.) Responsible officials of Crest Laboratories personally performed each step in the manufacturing process. (App. 39.)

On the same day, using the same work sheet, another batch of tablets was made up in identical fashion but with the estradiol omitted and each step in the manufacture again performed by the same officers. Samples of both batches were sent on the same day to Dr. Robert E. Hoyt at the Cedars of Lebanon Hospital in Los Angeles. We digress for a moment to point out the misconception of the Court as to the nature and probative value of the defense evidence concerning the manufacture of those experimental batches and subsequent experiments, which will be related by Dr. Hoyt in conjunction with Dr. Sobel. These experiments were carried out for the purpose of demonstrating that by following the U. S. P. method

of assay when 22 mcgs. of estradiol per tablet is used in combination with the corresponding great mass of excipients, that small amount cannot be extracted and estimated. The Court ruled such testimony to be inadmissible and we refer to that phase of the case more fully in our argument. This matter was argued at considerable length, the Court stating that he was not interested in any test made at a later time of some experimental tablet even though composed in the same way. It was only after counsel for the Government withdrew his objection that the Court reluctantly admitted the evidence in the record. [App. 38, 39; R. 115-126.] Dr. Hoyt possesses qualifications such as will not usually be found. He has been a teaching fellow and instructor at the University of Minnesota Medical School, instructor in the School of Medicine at U. C. L. A., Director of the Institute of Experimental Medicine, College of Medical Evangelists in Los Angeles. His function at the latter institution was to carry out experimental studies in medicine and related fields, and to supervise and perform laboratory procedures considered too delicate or difficult for average laboratory personnel to carry out properly. Presently he is Assistant Clinical Professor in the Department of Infectious Diseases at U. C. L. A. and during the war he lectured at the U. S. C. Medical School in the Department of Bacteriology and has written and published about 35 papers dealing with scientific subjects, one of which had to do with the evaluation of an assay procedure for a product related to estradiol. (App. 39-41.)

He and Dr. Sobel, also of the Cedars of Lebanon Hospital, worked side by side in the conduct of these experiments, and their full testimony as to the experi-

ments conducted by them appears in detail in the Appendix. We shall simply hit the highlights of it at this point. (App. 41-51.)

Their first problem was to discover how much pure estradiol could be extracted without the presence of excipients in following the U. S. P. procedure and they found that in doing so there was a loss of 27½% of the pure estradiol during the procedure when assayed without anything else in combination with it.

There was introduced into evidence for illustrative purposes a chart prepared by Dr. Hoyt for the purpose of illustrating the experiments conducted. That was received as Exhibit "I."

Next they took a quantity of the experimental batch received from Crest, labeled to contain 23 mcgs. When run by the U. S. P. method it was found that only 10.1 mcgs. of the 23 were recovered. Then after making correction for the known loss of 27½%, a recovery was represented of 13.8 mcgs. instead of 23, or 40% non-recoverable. (App. 41-43.)

Then they took samples of the experimental batch received from Crest which did not contain any estradiol. They ground these up and added a specific known amount of estradiol—20 mcgs. This amount was selected for the purpose of convenience and would make no difference in the final result whether 20, 22 or even 30 mcgs. had been selected. (App. 43-44.)

After these tablets were ground up and the estradiol added and the assay run, they made a recovery of 10.1 mcgs., or 50%. Then after correcting for the known loss of 27½%, the recovery amounted to 13.8 instead of 20, or 31% lost or nonrecoverable in the assay pro-

cedure. It was then his conclusion that some of the estradiol had been held or adsorbed on the excipients. (App. 44.) Carrying the experiment further, he took some of the tablets which contained 23 mcgs. of estradiol, ground them and placed them in what is known as a Soxhlet extracting device and extracted continuously from 12 to 18 hours with ether. This is not a procedure provided for in U. S. P. but he followed this method to see if more estradiol is recoverable than by the U. S. P. method. In so doing he was able to recover more than he had under the U. S. P. method, namely, 16.4 mcgs. (App. 44-45.)

Dr. Hoyt in detail explained the effect of adsorption by excipients on the estradiol. (App. 45-47.) He and Dr. Sobel did not run tests of the residue, as did the Government witnesses, namely, four additional extractions than those called for by the U. S. P. method because the method did not provide for it and they were retained to determine whether the amount of estradiol known to be present could be extracted, not to devise some method of assay which might be suitable. (App. 47.)

We refer the Court to Dr. Hoyt's testimony as it appears in the Appendix for the detailed discussion given by him on the subject of his experiment and his conclusions. (App. 39-48.)

Dr. Harry Sobel, who collaborated with and ran tests in duplicate with Dr. Hoyt, possesses an extensive educational background and experience, his specialty being a group of compounds which go into the making of certain hormones related to estradiol and he has written thirteen scientific papers, eight of which directly or indirectly had

to do with the subject. We refer the Court to that portion of the Appendix in which Dr. Sobel's testimony appears for a more detailed review of it. However, his testimony was largely cumulative of Dr. Hoyt's, with some expansion of it. (App. 48-51.)

IV.
THE QUESTION INVOLVED.

The sole question involved on this appeal is whether as a matter of law all of the substantial evidence in the case is as consistent with a reasonable hypothesis of innocence as with guilt.

V.
SUMMARY OF ARGUMENT.

It is academic that a question of law for the Court of Appeals to determine is presented when it is claimed that the evidence is insufficient to sustain the judgment, or, in other words, when it is claimed that there is no substantial evidence to support the judgment.

Whether there is sufficient evidence depends upon whether all of the substantial evidence is as consistent with innocence as with guilt. By this is not meant that the function of the jury, or a trial court sitting without a jury, to weigh the evidence and judge the credibility of the witnesses shall be in the leastwise impaired.

Substantial evidence has been defined by the Supreme Court in *N. L. R. B. v. Columbian Co.* (1939), 306 U. S. 292, 300, to be:

> "* * * more than a scintilla and must do more than create a suspicion of the existence of the fact to be established. It means such relevant evidence

as a reasonable mind might accept as adequate to support a conclusion. * * *"

Unimpeached credible evidence may not be disregarded by the trier of the facts in arriving at a verdict or judgment.

It is the unqualified position of the defendants in this case that there is no substantial evidence in the record consistent with any reasonable hypothesis but that of innocence. It is the defendants' position also that at the very most there exists no more than a mere suspicion that the products involved were adulterated and misbranded—below their labeled potency. This suspicion itself cannot even exist unless one is led to suspect that by reason of the Government's assays the products in question were below their labeled potency at the time of shipment and it is at the time of shipment that the offense was created or it never existed. The evidence of the Government was simply that they had assayed certain samples of the products involved under the U. S. P. method and did not recover the labeled potency; that they then deviated and made four additional extractions than those called for by U. S. P. and were unable to recover any estradiol; that they then added 200 mcgs.—10 times the labeled potency of these products—to the residue and attempted to extract it and recovered approximately 97% of that put in; that they then attempted to simulate the tablet in question but did not use the same ingredients, used one ingredient that was not even in the Woodard tablets, never followed the elaborate manufacturing processes involved or any process to complete a tablet in finished form and then simply taking the powdered substance, added 200 mcgs. of estradiol and were able to recover it.

This testimony simply assumed that by composing the ingredients in the form above mentioned a product equal to the Woodard tablets would be the result. Then they asked the Court to presume that the tablets in question did not contain 22 mcgs. each of estradiol at the time of shipment.

On the other hand we have the undisputed testimony, corroborated by the uncontradicted work sheets used in the manufacture of the Woodard tablets showing precisely the ingredients contained therein, the amounts, including the estradiol, in which case 5% more estradiol was used than called for to make tablets of 22 mcg. potency. In addition to this, it was conceded by the Government witnesses that estradiol does not lose its potency by lapse of time or being subjected to heat, in other words, it is stable. The experts for the defense were in agreement with the experts for the Government that from tablets, such as these, mixed in combination with the great mass of excipients, no more than approximately 14 mcgs. were extracted by the U. S. P. method.

Having already shown by uncontradicted evidence that the labeled amount of estradiol was in the tablets at the time of shipment, the defendants went further and by experiments which remain uncontradicted, showed that tablets made in precisely the same fashion as the Woodard tablets, with the same ingredients and in the same amounts, did not permit recovery of the labeled potency of 22 mcgs. even though Dr. Hoyt, who conducted the experiment himself, placed in the tablets 22 mcgs. of

estradiol. Dr. Hoyt showed without contradiction that even after correcting for a known loss that he demonstrated would occur, 30% of estradiol that he had placed in the tablets was not recoverable under the U. S. P. method.

In addition to the foregoing, the Court misconceived the applicable principles of law. First, it gave no probative value whatever to Dr. Hoyt's experiment because it happened to be an experiment of tablets prepared for that purpose at a time subsequent to the shipment involved notwithstanding the fact that these tablets were made as above stated. There can be no escape from this conclusion as it appears in the record itself and is more fully referred to in the argument which follows. Secondly, the Court was of the belief that if the defense position was that the U. S. P. method—even though it was the official method—was not accurate, the burden was upon the defendants to devise some test or assay method which would be suitable, entirely overlooking the fact that *the burden was upon the Government* to prove that by the U. S. P. method of assay the full amount of estradiol in such tablets could be assayed correctly.

The evidence in the case permits of only one conclusion and that is that the tablets involved contained the labeled potency at the time of shipment and that the U. S. P. method of assay, which is the official method, did not permit recovery of all of the estradiol present and that in reaching the conclusion that it did the Court erroneously applied principles of law which were vital to a proper determination of the case.

VI.
ARGUMENT.

(1) There Is No Substantial Evidence in the Record Consistent With Any Hypothesis but That of Innocence.

A question of law for the Court of Appeals to determine is presented when it is claimed that there is no substantial evidence to support the judgment or, said in another way, that the evidence is insufficient to sustain the judgment.

This of course is not the same thing as saying that the evidence for the defendants outweighs the evidence of the Government for it is academic that the weight of the evidence and the credibility of the witnesses is for the trier of the facts to determine. It is only when it is claimed that there is no substantial evidence to support the judgment that a question of law is presented.

Under the authority of countless cases, whether the evidence is sufficient to sustain the judgment depends upon whether all of the substantial evidence is as consistent with a reasonable hypothesis of innocence as with guilt. We shall cite only a few of the cases in support of this proposition. This principle, however, has been recognized by all of the circuit courts, later the courts of appeal, including this Court.

Isbell v. United States (C. C. A. 8th, 1915), 227 Fed. 788, 792;

Karn v. United States (C. C. A. 9th, 1946), 158 F. 2d 568, 570;

McCoy v. United States (C. C. A. 9th, 1948), 169 F. 2d 776, 783, 786.

The definition of substantial evidence was stated by the Supreme Court in *N. L. R. B. v. Columbian Co.* (1939), 306 U. S. 292, 300. (See p. 18 *supra.*)

There is another principle which is academic, that unimpeached credible evidence may not be disregarded by the trier of the facts. (*Texas Co. v. Hood* (C. C. A. 5, 1947), 161 F. 2d 618, 620); *Cruse v. Union Central Life Insurance Co.* (D. C. E. D. Tex. 1945), 59 Fed. Supp. 504, 506.)

An excellent statement of the rule is also found in *Chan v. T. I. & T. Co.* (1945), 107 Adv. Cal. App. 615, 620.

> "It is the general rule that the trier of fact cannot arbitrarily disregard uncontradicted, entirely probable testimony of an unimpeached witness. (*Mantonya v. Bratlie,* 33 Cal. 2d 120, 127 (199 P. 2d 677); *Fidelity & Casualty Co. v. Abraham,* 70 Cal. App. 2d 776, 782 (161 P. 2d 689).) Testimony which is not inherently improbable and is not impeached or contradicted by other evidence must be accepted as true by the trier of fact. (*Dobson v. Dobson,* 86 Cal. App. 2d 13, 14 (193 P. 2d 794).)

The credibility of the witnesses involved in this case is not an issue. Up to a certain point the experts for the Government and those for the defense were in agreement. They were in agreement that in assays conducted by them under the U. S. P. XIV method the labeled potency of 22 mcgs. was not *recovered.* The amount actually recovered by the Government experts ranged from 6 mcgs. to 16. The amounts actually recovered by the defense experts, following the same method, ranged from 9.1 mcgs. to 14½. They were not in agreement, however, as to

the reason for this small recovery. The inference from the testimony of the Government experts was that the small recovery was due to the fact that there was no more estradiol in the tablets at the time of shipment than the amounts recovered by them. The experts for the defense, on the other hand, testified that in their opinion the reason for the small recovery by them was the presence of such an infinitesimal amount of estradiol in the presence of such a tremendous mass of excipients, the ratio being 22 to 324,000 and that a quantity of the estradiol sufficient to make that difference became adsorbed onto the solid surfaces of the excipients and that it simply was not extractable under the U. S. P. method. Had this been the extent of the testimony it would have amounted to no more than a conflict and no question of law would have been presented to this Court. However, the evidence went farther.

The witnesses for the Government were men who had participated largely in the formulation of what became known as the U. S. P. XIV assay method for estradiol tablets, which method became official for the first time November 1, 1950. In an effort to demonstrate the accuracy and applicability of this method of assay to a product such as this, they conducted four extractions *additional* to those provided by the U. S. P. method, the purpose being to try and recover all of the estradiol present in the mass and were unable to recover any more. (App. 14.) This of itself of course *does not prove that the estradiol was not there* or that the extraction method was effective to extract all of it. With respect to the products involved in Counts V and VI, Dr. Banes, a Government witness, testified that the recovery was so low that he ran a further test with a Soxhlet device and recovered no

more estradiol. (App. 14.) This, however, simply confirms the testimony of Dr. Hoyt, the defense witness, that even with the Soxhlet device which he used in connection with the tablets in which he had placed a known amount of estradiol, there was *30% less recovery than he himself had placed in the mixture.* Then as to Counts VII and VIII, Dr. Banes testified that after making 4 extractions called for by the U. S. P. method, and 4 additional ones, he added to what was left 200 mcgs. of estradiol and recovered 97% of it. (App. 15.) This, however, is no proof at all that had he simply put in 22 mcgs., the amount involved in the tablets here, he could have *recovered* it and this is in the face of the testimony of Dr. Hoyt who did exactly that and was unable to recover more than 70% of what he had personally put in.

Finally, the Government simulated tablets in powdered form containing some but not all of the ingredients contained in the tablets in question, using an amount to correspond to the average weight of the tablets in these samples; used ten times that quantity to correspond to the tablet provided for in the U. S. P. assay method and then added 200 mcgs. of estradiol. (App. 15, 16, 18.)

It is true that in the simulated experiment conducted by the Government experts they said that they were able to recover the 200 mcgs. that had been placed in the powdered mixture. This testimony is far from being evidence that the tablets involved here did not contain the labeled amount of estradiol or that the U. S. P. assay method is suitable and accurate for the assay of them.

In the Government assay the same ingredients were not used, for instance, magnesium stearate instead of sterotex.

Also all of the ingredients used in the Woodard tablets were not used in the powdered mixture made up by the Government. Then the Government's mixture remained in powdered form and was never compressed into a tablet or carried through the manufacturing process necessary to produce a finished tablet. These processes were many and varied. First they were mixed in a standard pharmaceutical mixing machine and wet granulated to the point that a material of suitable mesh in density was prepared. This wet mass was then extruded and fed on tracings to dry. [R. 113, 114, 147.] Once the mass is wet it is withdrawn and put through a granulator, a machine that produces an extrusion resembling macaroni. The extruded material is then placed upon trays and put in a drying oven. It is then withdrawn and ground through a Stokes oscillator, which forces the granules or extrusions through a screen to produce the granulation of a definite mesh. Then it is again introduced into a mixer and mixed, at which point additional materials, lubricants, are added, well mixed, the material withdrawn and put onto rotary type tablet presses. The material falls into the cavity of a die where two punches are made to come into the die entrapping the material between the two punches and pressure is applied which forms the tablet. [R. 147, 148.]

When it is remembered that the witnesses for the Government and the defendants both conceded that when estradiol came into contact with solid surfaces a molecular change took place by which the estradiol became adsorbed on the solid surfaces of the excipients, it is of the utmost importance from any determinative standpoint in simulating a product such as the one involved not only to use exactly the same ingredients in the same quantities as those used in the manufacture of the Woodard tablets

but as well to put the simulated product through exactly the same manufacturing steps as the Woodard tablets. Without that being done, the conclusion following from the simulated experiment does not and cannot constitute "substantial evidence."

It simply amounts to using something different and doing something different than was done with the manufacture of the Woodard tablets and presuming, without any supporting testimony, that the difference was immaterial. Certainly this evidence of the simulated experiment of the Government cannot be considered substantial and inconsistent with any hypothesis of innocence in view of (1) the uncontradicted testimony of Galindo as to the constituents of the Woodard tablets, supported by the very work sheets from which they were manufactured showing the exact quantities that were used, all of which made up a tablet containing 22 mcgs. of estradiol plus a 5% overage, and (2) the uncontradicted testimony of Drs. Hoyt and Sobel wherein they used not a mere simulated powdered mixture, but a tablet made from the same work sheets as were the originals and which tablet contained exactly the same constituents in exactly the same amounts and made exactly in the same way as the ones in question, to which these doctors added an amount equal to 22 mcgs. of estradiol per tablet, assayed it according to the U. S. P. method, and recovered but approximately 70% of the amount known to be put in.

It is true that the admissibility of experiments lies largely within the discretion of the trial court but, even though admitted, does not render it "substantial evidence" or that which is beyond mere suspicion. (See *N.L.R.B. v. Columbian, supra,* p. 18.) Here the Government's experiment was vastly different than that attending the

manufacture of the Woodard tablets. The Government's experiments simply *presumed* that when the mixture was made up by its experts, it would be the same as the Woodard tablets. From this presumption the Court was asked to presume or infer something else; that therefore the U. S. P. method was accurate for the Woodard *tablets* and that the Government's assay results showed them to be below the labeled potency and that they were therefore below that potency at the time of shipment. This is no more than presuming one fact and then basing another and other presumptions on it. As said in *Texas Co. v. Hood, et al.* (C. C. A. 5, 1947), 161 F. 2d 618, 620, quoting from another case:

> " 'Neither the pleadings nor the proof can be left open to conjecture and guesswork. A presumption of a fact cannot rest upon a fact presumed.' "

The mixture made up by the Government, as we have said was not the same as the Woodard tablets. It had one constituent not contained in the latter and omitted other constituents contained therein. In addition, it remained in powdered form and was never put through the elaborate manufacturing process by which a compressed, finished tablet is made. This process of course is extremely important in that the more constant contact between the estradiol and the excipients the more adsorption takes place and consequently the difficulty of extraction in the assay procedure increased.

We wonder why the Government conducted these tests in addition to the U. S. P. method. If, as their experts would have the Court believe, that method was the most accurate in existence (App. 17), seeking to justify that method seems to indicate doubt in their minds as to its

accuracy when applied to a 22 mcg. tablet, otherwise they would have relied on the official method as being not only the legally recognized method but as well that which they said was the most accurate for the assay of any estradiol tablet.

There has never been any contention by defendants that the U. S. P. method of assay was not suitable or accurate for a tablet containing 200 or 220 mcgs. of estradiol. The defense theory was simply that it was wholly unsuitable, inaccurate and meaningless when it came to assaying for estradiol content a tablet containing 22 mcgs. of estradiol in combination with a large bulk of excipients of the kind and quantity contained in these tablets.

At the outset there exists the testimony of Mr. Galindo of Crest Laboratories, the manufacturer of the tablets. Through him the work sheets used in the manufacture of these products, Exhibits B, C and D, were introduced. His testimony remained uncontradicted and unimpeached that these tablets were manufactured according to standard pharmaceutical practices in the manufacturing field and that the materials shown on the work sheets in the corresponding quantities as shown thereon were used in the manufacture of these tablets and that a 5% overage of estradiol was used. The Government conceded by its own witnesses that estradiol does not lose its potency by reason of lapse of time or being subject to heat. The uncontradicted fact then remained clear through to the end of the trial that estradiol, a stable product, in an amount 5% more than was necessary to equal 22 mcgs. per tablet was used in the manufacture of these tablets. Necessarily in rendering its judgment the Court ignored this evidence which it was not at liberty to do.

This uncontradicted testimony was conclusively proved by the work sheets themselves, Exhibits B, C and D, which show what went into the manufacture, and how much.

It is academic that uncontradicted, credible evidence may not be disregard by the trier of the facts. In *Texas Co. v. Hood* (C. C. A. 5, 1947), 161 F. 2d 618, 620, the Court said, quoting from another case:

> " 'Although the circumstances may support the inference of a fact, if it is shown by direct unimpeached, uncontradicted, and reasonable testimony which is consistent with the circumstances that the fact does not exist, no lawful finding can be made of its existence. Pennsylvania R. Co. v. Chamberlain, 288 U. S. 333, 53 S. Ct. 391, 77 L. Ed. 819; Winn v. Consolidated Coach Corporation, 6 Cir., 65 F. 2d 256; citing cases.'
>
> "See Bonner v. The Texas Co., 5 Cir., 89 F. 2d 291; Cruse v. Union Central Life Insurance Co., D. C., 59 F. Supp. 504; Mutual Life Insurance Co. of New York v. Sargent, 5 Cir., 51 F. 2d 4; Deposit Guaranty Bank & Trust Co. v. United States, D. C., 48 F. Supp. 369; and Stone v. Stone, 78 U. S. App. D. C. 5, 136 F. 2d 761."

As heretofore stated and as appears in the Statement of Facts in the Appendix, concurrently with the manufacture of the 22 mcg. tablets, there were manufactured for Woodard by Crest quantities of 110 mcgs. tablets and the work sheets used in the manufacture of the latter were received in evidence as Exhibits E, F and G. With both the 22 and 110 mcg. tablets exactly the same ingredients from the same containers and in the correspond-

ing amounts were used and this includes as well the estradiol itself. No claim has been made by the Government at any time that the 110 mcg. products were below the labeled potency. This fact is important for this reason: It certainly may be assumed that if there had been any question about the potency of the 110 mcg. product a charge would likewise have been made against it. The defense theory as it appears throughout the record was that the U. S. P. method of assay may be effective in the assay of tablets of a higher potency such as a 110 mcg. tablet or one containing the equivalent or 200 mcgs. mentioned in U. S. P., but that the assay method is not in any sense accurate or suitable when it comes to the assay of a product containing but 22 mcgs.

The results of the tests conducted by the Government witnesses amounted simply to this: That they recovered no more than the amounts to which they testified. Whether any was left behind and was not extracted and therefore not possible of estimation at the end of the assay they did not know and the matter rested simply in their opinion that they extracted all that there was to extract. This involved wholly unwarranted assumptions. On the other hand, Dr. Hoyt, using tablets prepared in identically the same fashion as those in question, with the same ingredients and exactly the same amounts, found that there was unextractable 30% of what he had personally put into the tablets, all for the purpose of finding out whether the U. S. P. method would permit recovery of 22 mcgs. in combination with the excipients involved. Lastly, the uncontradicted evidence of Mr. Galindo, and as shown by Exhibits B, C and D, is conclusive that the labeled amount was actually put in the tablets *and there at the time of shipment.*

Under this evidence, therefore, the conclusion is inescapable that there was no substantial evidence that the Woodard tablets were below the labeled potency as charged, but on the other hand all of the substantial evidence pointed unerringly to the fact that these tablets were manufactured with the required amount in them and that the U. S. P. method of assay is wholly unsuitable and inaccurate for the assay of a *tablet* containing the constituents that these had and but 22 mcgs. of estradiol per tablet.

(2) The Trial Court Misconceived and Misapplied Certain Controlling Legal Principles.

(a) The Trial Court Considered the Evidence of Drs. Hoyt and Sobel to Be of No Evidentiary Value.

During the testimony of Mr. Galindo and preparatory to laying the foundation for the experiment conducted by Drs. Hoyt and Sobel with tablets identical to the ones in question and into which they placed a quantity of approximately 22 mcgs. of estradiol, counsel for the defendants asked Mr. Galindo concerning the preparation of a work sheet for these experimental batches, one prepared with the estradiol included and one prepared the same way but with the estradiol omitted. At this point the work sheet prepared by Crest Laboratories and Mr. Galindo for that purpose was offered into evidence as Exhibit "H" and bore a control number assigned for that purpose of 2571-B. This offer was objected to on the grounds that it was of something done subsequent to the manufacture of the tablets in question, presumably made up and sent out for analysis, all of which would have no probative value. This objection was sustained and the admissibility was argued by defendants' counsel, pointing out that it was not in-

tended to develop through Mr. Galindo the assay results of someone else but simply to lay the foundation by showing the manufacture of the tablets and then the result of the assay would be testified to by the person who made it. This discussion consumes pages 114 to 127 of the record. In connection with this the Court said on page 117, in sustaining the objection and speaking to defendants' counsel:

> "Even under your theory, while of course, you might offer expert testimony here of other chemists and as a basis for their opinion they might state that they had made such investigation and such tests, *that does not mean that they are admissible in evidence.* I assume that you are arguing that they have made some." (Italics supplied.)

On page 119 of the record, in referring to tests made of tablets prepared subsequent to the ones in question, and for the purpose of testing the validity of the U. S. P. method, the Court said:

> "But, you see, as I stated before, as far as this test is concerned, that they have made, this witness takes the stand and apparently has testified as to the amount of alpha estradiol that was placed in the particular tablets that are here in question.
>
> "Mr. Elson: That is right.
>
> "The Court: *But it doesn't go to prove the amount of alpha estradiol that was in the tablet itself at the time of shipment,* in other words, the question that we have to determine here, because of course the Court is faced with this position, if his testimony that that ingredient was placed in there is conclusive of the fact that it was in there at the time of shipment—
>
> "Mr. Elson: I do not mean that. That isn't my purpose.

"The Court: Well, at any rate, the point of course is that the only place where the testimony has any value is where the expert himself testified. You say you are going to call these exhibits." (Italics supplied.)

Here the Court was stating that the uncontradicted testimony of Mr. Galindo that the requisite amount of estradiol was placed in the tablets at the time of manufacture, and as further shown by the work sheets had no probative value to show that it was there at the time of shipment and that the only way in which this fact could be shown would be by testimony of experts. This misconception of the evidence was vital for it was testified and conceded by the Government experts that estradiol is a stable product and does not lose its potency by lapse of time or by being subjected to heat. Therefore under the evidence the fact remained uncontradicted throughout the entire trial that the requisite amount was put into the tablets at the time of manufacture from which it necessarily followed that it was in there at the time of shipment and for that purpose no testimony of an expert was necessary to show that it was there.

Coming back to the foundational examination on page 120 of the record, the Court stated that Mr. Galindo could testify as to the ingredients used in these experimental tablets but that:

"The mere fact that someone wanted him to make a test—and apparently that is the background of this here, to establish that he was requested by someone to make a test, who made out a work sheet, and it isn't necessary for him to put the work sheet in—*doesn't mean a thing.*" (Italics supplied.)

On the contrary it meant everything for it was the documentary proof prepared at the time that the batch was made, of the constituents of the tablets placed in the experimental batch as well as their quantities! It would be one thing for a witness to simply testify that certain chemicals had been placed in a mixture and in certain amounts and quite another thing for that witness to have ready for introduction into evidence the documentary proof that it was done.

Continuing in this discussion counsel for defendants pointed out that these tablets were delivered to an expert for analysis for the purpose of determining the amount of estradiol in them and, if so, how much. With regard to the test of the expert the Court said on page 121:

> "The Court: *Well, I am not interested in his test, I am not interested in a test of some subsequent tablet which was made, because it is not material here.* If he has made a test of these particular tablets and then he is going to testify as to these particular tablets, as has been done by the chemists who have testified here now, of course that goes to the question as to what was in those particular tablets. If he did not have and has not made a test of those particular tablets, if he is an expert that is going to testify here and not because someone told him there was a certain thing in a tablet, if he merely took a tablet and made an examination and analysis and tests with that particular tablet, his testimony, *as far as his testimony is concerned, would be entirely immaterial, because it is a different tablet.*" (Italics supplied.)

Following this discussion an offer of proof was made and objection sustained to it. Whereupon counsel for the Government undoubtedly realizing that the exclusion of

this offer of proof would constitute reversible error, withdrew his objection.

The foregoing demonstrates by the cold record itself that in the mind of the Court the assays made by Drs. Hoyt and Sobel of the experimental tablets were of no evidentiary value whatever.

It is true, of course, that a trial court is presumed to apply the correct principles of law but when the record shows exactly the contrary, this presumption falls to the ground.

In *United States v. Forness* (C. C. A. 2, 1942), 125 F. 2d 928, the court said at page 942:

> "* * * The correct finding, as near as may be, of the facts of a law suit is fully as important as the application of the correct legal rules to the facts as found. An impeccably 'right' legal rule applied to the 'wrong' facts yields a decision which is as faulty as one which results from the application of the 'wrong' legal rule to the 'right' facts."

In *Todorow v. United States* (C. C. A. 9, 1949), 173 F. 2d 439, the court said at page 448:

> "Clearly, no one incident is sufficient to warrant reversal, and to determine whether, in the aggregate, they adversely affected the substantial rights of the appellants, it is necessary to consider them in their natural and proper setting, namely, the entire record."

In *Fotie v. United States* (C. C. A. 8, 1943), 137 F. 2d 831, the court said at page 839:

> "Ordinarily in the trial before a court without a jury, the presumption is that the judge discards immaterial evidence, but that presumption must yield to a showing to the contrary."

It is plain from the foregoing that by the very statements of the Court, the testimony of Drs. Hoyt and Sobel was accorded no probative value at all. This testimony of course was not for the purpose of establishing that 22 mcgs. of estradiol were in the tablets involved *at the time of their shipment,* but rather to show that a tablet of such a low potency and containing the excipients that it did and their respective amounts as shown by the work sheets, did not permit a recovery of all of the estradiol present and therefore the U. S. P. assay was unsuitable and inaccurate and it is obvious that this substantial evidence of the defense was ignored by the Court in deciding the case and having been ignored erroneously, requires a reversal of the judgments.

(b) The Trial Court Erroneously Adopted the View That Any Method of Assay, Whether U. S. P. or Not, Was Admissible and Valid.

During the final argument, counsel for the defense called the Court's attention to Section 501 (b) of the Federal Food, Drug and Cosmetic Act (21 U. S. C., 351 (b)) stating that under that section when a drug becomes recognized in an official compendium, such as U. S. P., and provides a method of assay for that drug, that assay and that alone is the only one that can be considered as having any evidentiary value. The Court stated that he had examined that section and did not see what difference it made and that the most effective way for the defendants to defend their case and show that the U. S. P. method was not suitable was by showing that there were 22 mcgs. in the tablets in question. [R. 305, 306.] During the course of the argument the Court also pointed out that he had asked Dr. Hoyt whether if the tablets had been

submitted to him for analysis they could have been accurately assayed as to the number of micrograms in them. [R. 304, 305.] Dr. Hoyt, during this questioning, stated that he was sure it could be done perhaps by a biological method of assay, which, however, is not the U. S. P. method. This misconception by the Court of what was permissible proof under Section 501 (b) of the Federal Food, Drug and Cosmetic Act (21 U. S. C., Section 351 (b)) involving, as it necessarily did, on whom the burden of proof rested, was a vital misconception which led the Court to rule that the defendants, having not introduced evidence of some assay, whether it was U. S. P. or not, showing that the tablets in question had 22 mcgs. in them, amounted to a failure of proof.

Under the very terms of 21 U. S. C. 351 (b) a drug is misbranded if it is a drug that appears in an official compendium and its strength falls below the standard set forth in such compendium, and the determination as to its strength or quality shall be made according to the method of assay set forth in that compendium. All of Section 351 (b) appears in the Appendix. (App. 56, 57.)

We have here, then, the fact shown by the record that for the first time the drug in question, alpha estradiol tablets, was recognized and appeared in an official compendium, namely U. S. P. XIV, on page 227, which became official November 1, 1950. The drugs in question were manufactured before that time. The assays conducted by the Food and Drug Administration of the products in question were made before that time. However, the Information here was filed May 8, 1951. [R. 21.] Therefore for a period of seven months prior to the filing of the Information the drug in question was recognized in U. S. P. and a method of assay provided.

It will be recalled that prior to the adoption of the U. S. P. method no method of assay for estradiol *tablets* had appeared in any official publication or in any of the scientific literature. In fact, Dr. Jeffreys of Truesdail Laboratories, one of the best known laboratories in Southern California, stated that prior to July 1950 he had been requested to run an assay of samples of the tablets involved, by Crest Laboratories and had refused to do so because no assay method had appeared up to that time for such tablets of such low potency. In July 1950 he had received his advance copy of the U. S. P. XIV which contained a method of assay and then proceeded to conduct the assays to which he testified. There had previously appeared what was known as the Kober method of assay but this method was for the assay of pure estradiol alone not in combination with any excipients and obviously, therefore, not suitable to the assay of a tablet.

A U. S. P. method of assay existed at the time of the filing of the Information and consequently at the time of trial whether or not the drugs in question were below their labeled potency or not could only be determined from a legal standpoint by the U. S. P. method and not some other. The burden was on the prosecution, therefore, to show that at the time of shipment of these products in August 1949, July 1949, January 1950 and April 1950, these drugs were below their labeled potency of 22 mcgs. and this determination could only be made by the U. S. P. method even though it was adopted subsequent to the dates of shipment. It cannot be said that because no official

method existed at the time of shipment *any* method of assay would be relevant to determine the question as the following analysis will disclose.

The Information did not charge a violation of 21 U. S. C., Section 351 (b) but of 351 (c). Under Section 351 (b) (App. 56, 57) a drug is adulterated if at the time of shipment it is recognized in U. S. P. and its strength, according to the U. S. P. assay method, is below the labeled potency. Under Section 351 (c) (App. 56) a drug is adulterated "if it is not subject to the provisions paragraph (b)"; that is, is not recognized in U. S. P. and its strength differs from that which it is represented to possess. A drug which is not recognized in U. S. P. and consequently no assay method provided may be assayed by any method selected. It could not have been charged that Section 351 (b) had been violated if the drug at the time of shipment was not listed or recognized in U. S. P. Therefore the situation presented here is a drug which is not "official" at the time of shipment becoming official seven months before the Information is filed and an official assay method for the first time then appearing. The question, then, is: At the time of trial may the question of adulteration or misbranding be determined by employing any assay method other than the official method?

It must be assumed, and the Government witnesses in fact testified, that the U. S. P. method was selected as the most accurate and suitable for estradiol tablets (App. 17.) It should be noted that 21 U. S. C., Section 351 (b) (App. 56, 57) provides that if the Food and Drug Administra-

tion is of the view that an assay method selected by the U. S. P. Revision Board is not suitable or accurate it shall bring that fact to the attention of the Board and if the Board does not make the change then the Food and Drug Administration by regulation can. No such regulation has at any time been adopted. Repeating, therefore it must be assumed that the U. S. P. method of assay was considered by the U. S. P. Revision Board and the Administration as the most effective assay method for such tablets as of and for several months prior to November 1, 1950.

An assay method, however, is merely a *means to determine whether a drug contains what it is represented to contain* and the basic question here is whether the drug involved contained 22 mcgs. of estradiol in each tablet at the time of shipment. *The question is not whether one assay method is more accurate than another.* 21 U. S. C., Section 351 (b) specifically provides that when an assay method is recognized in U. S. P. it is the official method and the question determined by following that method alone.

To say that the U. S. P. assay method does not apply to a drug shipped before its adoption and only applies to a drug shipped after its recognition in U. S. P. defeats the Federal Food, Drug and Cosmetic Act itself. This would necessarily mean that the U. S. P. method must be followed as to drugs shipped after its adoption but not to drugs shipped before; that it is accurate as to the former

but not the latter; that it is accurate and acceptable as to a drug shipped at one time and not as to one shipped at another. If of any value at all the U. S. P. assay method must be controlling as the method of assay to be used from the time of its adoption as to any such drug which is to be assayed regardless of when shipped.

Whether the drug was below the labeled potency at the time of shipment has nothing to do with the assay method employed. The drug was or was not below that potency at the time of shipment regardless of the assay method.

If a drug was shipped before the U. S. P. assay method was adopted and assayed by some method selected by the chemist and found to be equal to the labeled potency, and then the U. S. P. method became official and the drugs assayed by that method and found below the labeled potency the latter would necessarily control because it has been adopted as the official and best and only method for the determination of that question. The difference between the two results could have no more legal effect upon the question of adulteration than this: That at the time of shipment the shipper believed, and had reason to believe, that the drug was not adulterated. His belief or intent, however, is immaterial and the U. S. P. method of assay being the official method for determining the question of adulteration would necessarily control.

If some method other than the U. S. P. were relevant because the drug was shipped before it was recognized in U. S. P. and this other method showed the drug to be above its labeled potency but then the U. S. P. method

became official and an assay under it showed it to be below labeled potency, then in order for the former test to control it would of necessity have to be accepted that it was more accurate than the U. S. P. test to determine the question itself. This might seem to work an injustice on one who before shipment assayed a drug under a method then existing and found it to be equal to its labeled potency but, as we have said, an assay method is only a means of determining a fact and if the U. S. P. method is to be of any value at all it must be taken as the accepted and only method to determine that fact, whether or not the time of shipment was before the drug became official or not. Such a situation would warrant, and possibly would require a fair-minded prosecutor to dismiss the action, or the Court to impose a mere token fine. If this analogy were not true, then we would find ourselves in this impossible situation: In one court room a person could be tried for shipment of a drug made before it was recognized in U. S. P. and any assay method would be admissible to determine the fact of adulteration or misbranding, whereas in the next court room, and being tried at the same time, would be a person who had shipped after the drug was recognized in U. S. P., in which case only the U. S. P. assay method would be admissible to determine the very same fact. Hardly could it be said that the U. S. P. method would be accurate for goods shipped at one time but not accurate as to goods shipped at another. If the U. S. P. method would not be valid in one case but would in another, then it could hardly have any valid basis for conviction in any case.

Any deviation from the U. S. P. method simply would not be that method. It could have no more validity than if made of a drug shipped after the method became official, for if such were the case then in any litigation on the subject the defendants would be enabled to show, and conversely the Government, that a drug was adulterated or not by reason of some assay method other than that provided by law.

It therefore necessarily follows that the one method of assay by which the question of potency could be determined was by the U. S. P. method of assay and that method alone.

The Court completely misconstrued the meaning and effect of 21 U. S. C., Section 351(b), and took the view that because Dr. Hoyt stated that he probably could assay these products correctly by some method other than U. S. P., he should have done so. This, therefore, simply amounted to placing upon the defendants the burden of devising an assay method which would be suitable for the assay of these products and which was not the U. S. P. method. Certainly no such burden existed or could exist.

The trial court confused the effect of the U. S. P. method upon the question before it in another particular as follows: At the opening of the defense argument, the Court stated that [R. 301]:

> "The question in the mind of the court is the absence of any testimony on the part of the defendants as to assays made by the defendants to determine the amount of alpha estradiol in these tablets."

The entire defense theory and all of its evidence was directed to the fact, first, that the requisite amount of estradiol had been placed in these tablets at the outset as shown by the testimony of Mr. Galindo and the work sheets and that the U. S. P. method of assay was unsuitable and inaccurate and determined nothing so far as these tablets were concerned. Obviously, the defendants were unable to present any assays made of *these tablets* showing the labeled potency to be in them because the U. S. P. method of assay could not and did not show it! It is true Dr. Jeffreys testified as to the amount that he recovered in his U. S. P. assay of some of these tablets and he stated the amount recovered was approximately 9 mcgs. as against a labeled potency of 22. But he stated that in his opinion all of the estradiol was not extracted and gave extensive reasons why. Further defense testimony was to the same effect, concluding with the experiment of Drs. Hoyt and Sobel that the legal method of assay—the U. S. P.—simply could not determine the amount of estradiol in these tablets. Again on page 304 of the record, during the argument, the Court specifically stated that the most effective way to prove that the U. S. P. method was not suitable and that the tablets in question contained the labeled potency was "to have men testify who used other systems, who, after making analyses, would tell you, for instance, that there were 22 micrograms in that tablet."

The Court here was of the erroneous view that the burden was upon defendants *to discover some method of assay* that would be suitable for these products so that

they could come into court and testify that they had discovered this method and by using it showed the required amount in the tablets. As we have said, there was no method known in the scientific literature for the assay of estradiol tablets of this potency and there was no method of assay at all for estradiol tablets appearing prior to the adoption of the U. S. P. method. How then could the defense, even if it were permissible as a matter of law, assay these tablets accurately except to experiment with some method or methods and then come into court and say that their method was accurate and the U. S. P.—official—method therefore inaccurate. The same view of the Court appears on pages 305 and 307 of the record and amounts simply to this: that if the defendants contended and showed by undisputed evidence as they did, that the U. S. P. method was inaccurate for the assay of these tablets, such evidence would have no probative value unless the defendants went further and assumed the burden of devising a method of assay which was accurate. Such a burden has never been and could not validly be imposed upon a defendant in a criminal case. The fact is that the U. S. P. method was the official and only method that was valid for determining the potency of these products whether they were shipped before or after the method became official and the only substantial evidence in the case on the subject showed conclusively that the labeled amount of estradiol was placed in the tablets and that the U. S. P. method was not determinative of the question presented.

VII.
CONCLUSION.

From the foregoing it follows that all of the substantial evidence is not consistent with guilt and is inconsistent with any reasonable hypothesis, but that of innocence. The misconceptions of the trial court mentioned led it to render the judgments and sentences, the one against Woodard Laboratories, Inc., being, according to our information the largest single sentence imposed against any single defendant in a food and drug case during the entire year of 1951. This extremely large fine of $2500.00 could only have resulted from the Court believing that the evidence of the Government showed the product to be below the labeled potency at the time of shipment. This evidence of the Government has been pointed out to create nothing more than a mere suspicion at the utmost. The misconception of the Court further led it to completely ignore the uncontradicted testimony which established as a fact that the products contained the labeled amount of estradiol, plus a 5% overage at the time of shipment and also led it to completely ignore, as inadmissible evidence, the experiments of Drs. Hoyt and Sobel which proved beyond question that under the U. S. P. method of assay *these products* containing no more than 22 mcgs. of estradiol in combination with 324,000 parts of excipients, could not be accurately assayed under the U. S. P. method for their estradiol content.

It therefore follows that by the record before this Court the judgments must be reversed.

Respectfully submitted,

EUGENE M. ELSON,
Attorney for Appellants.

APPENDIX.

STATEMENT OF FACTS.

(1) The Manufacture and Shipment of the Products Involved.

Woodard Laboratories ordered the estradiol used in the manufacture of the products involved either directly from International Hormones Company of Brooklyn, New York, or through its agent and broker, Silas & Company of Los Angeles. [R. 67.] The estradiol so ordered was not delivered to Woodard but shipped directly to Crest Laboratories of Burbank, California, who had been retained to manufacture the tablets into finished form. The manufacturing orders called for the manufacture of quantities of estradiol tablets each containing 22 mcgs. as well as a quantity of tablets each to contain 110 mcgs. [R. 68-71.] These tablets were manufactured by Crest Laboratories and delivered in bulk form to Woodard where they were packaged, labeled and shipped.

The estradiol furnished by International Hormones complied with the specifications called for by United States Pharmacopoeia, that is to say the pure estradiol had a melting range between 173 and 179 degrees and a specific or optical rotation between the range of 76 to 83 degrees. [R. 82.] (Vol. XIV, U. S. P., pp. 225 and 226.)

Joseph G. Galindo, Vice President and at the time of the manufacture of the products in question, production manager of Crest Laboratories, testified concerning the process and method of manufacture. Crest Laboratories is a private formula manufacturing company, that is to say they manufacture pharmaceutical products for other concerns such as Woodard Laboratories, to be marketed by the ordering concern under their own name and Crest

Laboratories does not sell or distribute any of the products they manufacture. [R. 98, 99.] The equipment used by Crest Laboratories is standard production equipment used in pharmaceutical manufacturing and they maintain as well an analytical library. [R. 99.] Mr. Galindo detailed his experience in pharmaceutical manufacturing and related subjects as follows: He attended the University of California at Los Angeles 1938-1940, majored in chemistry and attended a short course in chemical engineering at U. S. C. for six months in 1941. He became associated with Crest Laboratories in 1946 and has been with them ever since. [R. 100.] He belongs to the American Chemical Society, the American Pharmaceutical Association, the American Association for the Advancement of Science, the Medical Research Association of California, and the Institute of Food Technologists. One of his duties is the preparation of a publication known as "Crest Comments," the object of which is to disseminate some of the medical and pharmaceutical information appearing in the journals among the customers of Crest Laboratories, as well as anyone else interested and it is distributed to some of the largest manufacturers of pharmaceuticals in the world, *i. e.,* Squibb, Park Davis, Merck, etc. [R. 101.] The methods of manufacture employed by Crest Laboratories at the time the products in question were prepared were according to the accepted standards in the field. Mr. Galindo also makes trips East to consult with and study the methods employed by some of the largest pharmaceutical houses in order to keep abreast of new developments in the manufacturing field. [R. 102.]

Digressing for a moment and referring to the testimony of Mr. Sullivan, general manager of Woodard, it

is the uniform practice of pharmaceutical manufacturers and distributors to assign a "lot number" to all products which find their origin in a certain batch of material, for example, in connection with the products in question a certain batch or quantity will be manufactured and all tablets made from that batch or quantity will be assigned a certain lot number which will appear on the package in which the finished product is distributed. That was done in this case and Woodard assigned to the finished tablets received from Crest Laboratories manufactured from a particular batch their own lot number, for example, Woodard assigned Lot No. 497,567 to the products subject of Counts I, II, VII and VIII. [R. 67, 68.] They assigned Woodard Lot No. 897,618 to the products subject of Counts II and IV [R. 69] and Lot No. 107,694 to the products subject of Counts V, VI, IX and X. [R. 70.] With respect to Woodard Lot No. 497,567, Crest Laboratories assigned what is known as a "control number" to the batch from which those tablets were manufactured. They assigned control No. 2571 to the 22 mcg. tablets and control No. 2570 to the 110 mcg. tablets. (As heretofore stated at the time that Woodard ordered of Crest the manufacture of the 22 mcg. tablets to which Woodard assigned Lot No. 497,567, they also ordered the manufacture of a quantity of 110 mcg. tablets which, however, are not involved in this litigation.)

In connection with the products subject of Counts III and IV, bearing Woodard Lot No. 897,618, Woodard had ordered of Crest Laboratories the manufacture of a quantity of 22 mcg. tablets and a quantity of 110 mcg. tablets and Crest assigned to the manufacture of the 22 mcg. tablets control No. 2800 and control No. 2803 to the 110 mcg. tablets. [R. 104.]

In connection with the tablets bearing Woodard Lot No. 107,694 which are the subject of Counts V, VI, IX and X, Woodard had ordered the manufacture by Crest of a quantity of 22 mcg. tablets and Crest assigned its control number thereto of 3180. In connection therewith Woodard had also ordered the manufacture of a quantity of 110 mcg. tablets to which Crest also assigned control number 3181. None of the 110 mcg. products were charged to be below the labeled potency and are therefore not involved in the litigation. [R. 106.]

It should be borne in mind, however, that in connection with each order for 22 mcg. tablets Woodard also ordered the manufacture of 110 mcg. tablets which were manufactured in precisely the same way and with the same ingredients as were the 22mcg. tablets and the estradiol used was from the same bottle that contained the estradiol used in the manufacture of the 22 mcg. tablets. [R. 106, 107.]

Therefore comparing the lot number assigned by Woodard to the products involved in the respective counts and the corresponding control number given thereto by Crest Laboratories in the manufacturing process, we find the following:

Counts I, II, VII and VIII bore Woodard Lot No. 497,567 and Crest control No. 2571.

Counts III and IV bearing Woodard Lot No. 897,618 bore Crest control No. 2800.

Counts V, VI, IX and X bearing Woodard Lot No. 107,694 bore Crest control No. 3180.

In connection with the manufacturing process of each of the three batches involved in the counts as above referred to, Crest prepared what is known as work sheets. At the same time work sheets were prepared for the 110 mcgs. tablets. The preparation of such documents is standard pharmaceutical manufacturing procedure. [R. 107.]

The work sheet bearing Crest control No. 2571 which involved the corresponding Woodard control number 497,-567 (Counts I, II, VII and VIII) was introduced into evidence as Exhibit B. [R. 110.] Crest control No. 2570 was assigned the 110 mcg. worksheet. [Ex. E.]

The work sheet bearing Crest control No. 2800 which involved the corresponding Woodard Lot No. 897,618 and the products involved in Counts III and IV was introduced into evidence as Exhibit C. Crest control No. 2803 was assigned the 110 mcg. worksheet. [Ex. F; R. 110-111.]

The work sheet bearing Crest control No. 3180 which involved the corresponding Woodard Lot No. 107,694 and the products subject of Counts V, VI, IX and X was introduced into evidence as Exhibit D. [R. 111.] Crest control No. 3181 was assigned the 110 mcg. worksheet. [Ex. G.]

In connection with the work sheets for the manufacture of the products involved here and which constitute Exhibits B, C and D, an overage of estradiol

of 5% was used in each case, that is to say 5% more estradiol was used in the manufacture than called for to furnish a completed product with each tablet containing 22 mcg. of estradiol. [R. 112.] In the manufacture of each batch involved in the counts of the information, the steps employed were precisely the same, the ingredients the same and the quantities employed the same, the quantities, however, varying because more tablets were called for in some instances than in another. For example, Exhibit B shows the 45,285 tablets manufactured, whereas Exhibit C shows 100,000 manufactured. Consequently the proportionate amount of ingredients in the latter case would necessarily be correspondingly greater than in the manufacture of a lesser amount.

The steps used in the manufacturing process in each case were as follows: The individual materials called for by the work sheet were weighed separately by a weigh master and again checked individually to verify the exact weight. The materials were then turned over to the mixing department where they were again checked and then mixed in standard pharmaceutical mixing equipment. They were wet granulated. The estradiol was added and the wet mass extruded and fed on tracings to dry in a forced draft house and subsequently ground through a specified mesh and again mixed. [R. 113, 114.] It is a wet homogeneous mass. [R. 140.]

Lubricants are added and the mass is run through the tableting machine on rotary tableting presses. [R. 114.]

One of the reasons for providing for overages of materials in manufacturing is to compensate against loss of material in the manufacturing process that more or less naturally occurs. [R. 141.] A loss of some materials occurs principally by being blown off in the nature of dust. There is a loss in the punches or from the dies in the tableting machine and that is something that occurs always in the manufacturing process of such materials. [R. 150.] However, any quantity that is lost is a part of the homogeneous mass to which the estradiol has been added and mixed completely, and the solution wet throughout with that product so that if, for example, a certain amount is lost in the manufacturing process it is part of the homogeneous mass which cannot and does not affect the potency of the finished material or the quantity of any of its individual constituents. For example, if so much as one-half were lost the one-half remaining would still have in proportion the amounts of constituents called for by the work sheets but the end result would be that there would be only one-half of the amount of tablets than would have been the case if the other half of the homogeneous mass had not been lost. [R. 140.] The purpose of weighing the finished tablets after they have been tableted is not to determine the amount of the homogeneous mass that might have been lost but rather for the purpose of determining how many tablets have been manufactured. The tablets are not counted but are determined by weight after tableting, for the weight of one tablet is known. [R. 149.]

(2) Assays of Samples of the Products Are Made by the F. D. A. and the Results Thereof.

Samples of the products involved in Counts I and II (Woodard Lot No. 497,567, Crest control No. 2571) were obtained by an inspector of the Food and Drug Administration on September 2, 1949, and delivered to Jonas Carol for laboratory analysis and identified in part by the inspector by No. 29-794-K written thereon. [Ex. 1, pp. 1 and 2.]

Samples of the products involved in Counts III and IV (Woodard Lot No. 897,618, Crest control No. 2800) were obtained by an inspector of the Food and Drug Administration on February 9, 1950, and delivered to Mr. Carol for analysis. These samples were identified by the inspector by the number 49-677-K written thereon. [Ex. 1, p. 2.]

Samples of the products involved in Counts V and VI (Woodard Lot No. 107,694, Crest control No. 3180) were obtained by an inspector of the Food and Drug Administration on April 24, 1950, delivered to Mr. Carol for analysis and identified by the number 49-693-K written thereon. [Ex. 1, pp. 2 and 3.]

Samples of the products involved in Counts VII and VIII (Woodard Lot No. 497,567, Crest control No. 2571) were obtained by an inspector of the Food and Drug Administration on August 18, 1949, delivered to Mr. Carol for laboratory analysis and identified by the number 53-254-K written thereon. [Ex. 1, p. 3.]

Samples of the products involved in Counts IX and X (Woodward Lot No. 107,694, Crest control No. 3180) were obtained by an inspector of the Food and Drug Ad-

ministration on June 7, 1950, and delivered to Mr. Carol for laboratory analysis and identified by No. 88,164-K written thereon.

Jonas Carol, chemist for the United States Food and Drug Administration for 21 years and presently Chief of the Synthetic Branch of the Division of Pharmaceutical Chemistry was one of the two witnesses called by the Government to testify concerning the results of the assays of the samples in question. [R. 35, 36.]

Mr. Carol, as shown by the testimony, is a man of unquestioned experience who has written a number of papers in scientific journals on drug chemistry and chemistry of hormones and has done a great deal of work in the analysis of estrogenic hormones. He participates in the granting of doctors' degrees at Georgetown University on the subject of hormone chemistry or spectrophotometric analysis and consults with various chemists and commercial firms on the methods of analysis of hormones and he has analyzed or assayed drugs containing estradiol approximately 1,000 times. [R. 36-38.]

The United States Pharmacopoeia which publishes what is known as the U.S.P., meets periodically and has at all times various committees and groups devising standards for drugs, writing monographs describing drugs and tests that are to be made to establish their purity and composition and these tests are the regular tests for drugs if the test itself is to be found in U.S.P. An official U.S.P. method for the analysis of alpha estradiol tablets exists. He and his associates did experimental work and wrote the method of assay that appears under the heading "Alpha estradiol in Tablets" in U.S.P. U.S.P. XIV means the 14th revision of U.S.P. and that is the latest revision.

There are other ways of analyzing the quantity of estradiol in a tablet but each method would involve some way of extracting the estradiol from the tablet material or the excipients, and after extraction the quantity of estradiol extracted would be determined. [R. 39, 40.] The general process of extraction has been in use for at least 50 years and the earliest method by which the amount of estradiol extracted might be determined was first published in about 1933 or 1934. The U.S.P. XIV method is therefore an adaptation of methods that have been published; a refinement of them. This method is relatively simple compared to many hormone analysis. [R. 40, 41.]

With reference to the products subject of Counts I and II (Woodard Lot No. 497,567, Crest control No. 2571) he made an analysis of these tablets using an infra red procedure, which procedure is used after the extraction process has been completed, and he recovered 15 mcgs. of estradiol per average tablet as against the labeled potency of 22 mcgs. His recovery was 68% of the labeled potency and this analysis was made on or about January 20, 1950. He believes the infra red method is the most informative and definite available. [R. 42.] A portion of the same sample was reanalyzed on August 6, 1951, with the same result. The reason for the second analysis was to determine whether there had been any deterioration of the drug in the year and one-half that had elapsed from the first analysis and he found that it was unchanged. [R. 42, 43.]

With regard to the analysis conducted by him, in each instance there was involved an extraction procedure. In that process he used 6 portions of ether to extract the drug and then combined those six portions of ether, carried on

the analytical procedure to the end. After doing that on the same residue, he extracted six times more, combined these extractions, reanalyzed that portion and recovered no estradiol in the second combined extractions. [R. 44.] The witness then explained that in the extraction process the tablets, after being weighed, are powdered and an amount of the powder to contain the amount of active ingredient to be finally tested is weighed and suspended in water and placed in a separatory funnel. Then is added an emissible solvent which can be heavier or lighter than water. In his case he used ether, which is lighter. That is poured on top of the water in suspension of the tablet material and shaken. The active ingredient which is more soluble in ether than in water will pass into the ether. By use of a stop-cock at the bottom of the separatory funnel the water is drawn off and the alpha estradiol extracted remains in the ether. It is not expected that all of the estradiol will be extracted on the first extraction process, so the water is drawn off into a second separatory funnel. He would say that better than 90% would be extracted on the first extraction and on the second extraction; that is continued until no more water is left in the active ingredient.

He made a similar analysis of a sample of the product subject of Counts III and IV (Woodard Lot No. 897,618, Crest control No. 2800) and recovered 14 mcgs. of estradiol per tablet, or 63% of the labeled potency, which he reported on April 14, 1950.

He made a similar analysis of a sample of the product involved in Counts V and VI (Woodard Lot No. 107,694, Crest control No. 3180) and recovered 6 mcgs. of estradiol per average tablet, or 28% of the labeled potency, which he reported May 31, 1950. He reanalyzed that

sample on August 6, 1951, and recovered 5 mcgs. of estradiol per tablet, or 23% of the labeled potency.

He analyzed a sample of the product involved in Counts VII and VIII of the Information (Woodard Lot No. 497,567, Crest control No. 2571) and recovered 15 mcgs. of estradiol per average tablet, or 68% of the labeled potency which he reported January 20, 1950.

He analyzed a sample of the product involved in Counts IX and X (Woodard Lot No. 107,694, Crest control No. 3180) and recovered 6 mcgs. of estradiol per tablet, or 28% of the labeled potency, which he reported June 13, 1950. [R. 42-47.]

Analyses were also made by one of his associates, Dr. Edward Haenni, under his supervision. He gave Dr. Haenni three of the samples, which were samples of the products involved in Counts III and IV (Woodard Lot No. 897,618, Crest control No. 2800) and he analyzed those samples by the U.S.P. method and he recovered 14 mcgs. of estradiol per tablet, or 63% of the labeled potency on May 14, 1950. [R. 48.]

He also gave Dr. Haenni a sample of the product involved in Counts V and VI (Woodard Lot No. 107,694, Crest control No. 3180). He analyzed it by the U.S.P. method and recovered 7 mcgs. of estradiol per tablet, or 32% of the labeled potency which he reported May 31, 1950.

He also gave Dr. Haenni a sample of the product involved in Counts IX and X (Woodard Lot No. 107,694, Crest control No. 3180). He analyzed it by the U.S.P. method and recovered 7 mcgs. of estradiol per tablet, or 32% of the labeled potency which he reported June 13, 1950. Dr. Haenni followed the U.S.P. method exactly

and in addition on the initial extraction procedure, using chloroform as specified in U.S.P., he made four additional chloroform extractions, carried those through the U.S.P. procedure, and recovered no estradiol in them. [R. 48-50.]

Dr. Daniel Banes, a chemist with the Food and Drug Administration in Washington since 1939, and employed in the division headed by Mr. Carol, also testified. His chief work has been in research on the analysis of estrogenic hormone preparations since 1948 and he has specialized in drug analysis since 1940. [R. 51.] Dr. Banes obtained his Bachelor's degree in 1938, his Master's degree in 1940, and his Ph.D. at Georgetown University in 1950. His thesis in connection with the latter degree was on the natural estrogenic ketosteroids. He is a member of the Association of Official Agricultural Chemists, a member of Phi Beta Kappa, and an honorary society of Georgetown. He has written 12 papers dealing with the analysis of drugs, the last part of which have been concerned with estrogenic hormones. [R. 52.] He heard the testimony of Dr. Carol regarding the various methods of analysis, the period of time that the various methods have been in existence, etc., and his testimony he believes would be the same if the same questions were put to him as were put to Mr. Carol.

He received a sample of the product involved in Counts I and II (Woodard Lot No. 497,567, Crest control No. 2570) and analyzed it according to the U.S.P. XIV method. [R. 53.]

In developing the U.S.P. method his group tested a large number of samples containing various amounts of estradiol and convinced themselves that the number of extractions called for and the amounts used for analysis

would give a complete extraction of the estradiol and would permit an accurate assay for it. With regard to the use of chloroform in the extraction under the U.S.P. procedure, they were quite certain that with four extractions called for by that procedure it would extract all of the estradiol. [R. 54, 55.]

With regard to the samples of the product in question after all four of the extractions were made he reextracted the samples with four further portions of chloroform, evaporated the chloroform, went through the whole method prescribed by U.S.P., tested the second group of extractions and recovered a very negligible quantity of estradiol. [R. 55.]

He analyzed a sample of the product involved in Counts I and II (Woodard Lot No. 497,567, Crest control No. 2570) according to the U.S.P. method and recovered 16 mcgs. of estradiol or 73% of the labeled potency.

He similarly analyzed, according to the U.S.P. method, samples of the product involved in Counts III and IV (Woodard Lot No. 897,618, Crest control No. 2800) and recovered 16 mcgs. of estradiol, or 73% of the labeled potency. These analyses were reported by him April 6, 1951. [R. 57.]

He analyzed a sample of the product involved in Counts V and VI (Woodard Lot No. 107,694, Crest control No. 3180) and recovered approximately 7 mcgs. of estradiol, or 31% of the labeled potency. Since the recovery here was so much lower than the others, he crushed 30 tablets and put them in a thimble, a part of a Soxhlet extraction apparatus which will permit the continuous extraction of solid material. He described the process of this apparatus, and after 7 hours of extraction he tested the undissolved material for the presence of estradiol and recovered none.

He then took a portion of what was soluble in methyl alcohol, evaporated that and after evaporation went through the U.S.P. XIV method, and recovered about 7 mcgs. [R. 59, 60.]

He also conducted a test to determine whether any estradiol was destroyed in the heating process of the solvent and found that it was not.

He also analyzed a sample of the product the subject of Counts VII and VIII (Woodard Lot No. 497,567, Crest control No. 2571) by the U.S.P. method and recovered 16 mcgs. of estradiol per tablet, or 73% of the labeled potency.

With respect to a sample of the products involved in Counts IX and X (Woodard Lot No. 107,694, Crest control No. 3180), he recovered approximately 6½ mcgs., of 30% of the declared quantity and all those results were reported August 6, 1951.

With regard to the last analysis, after making the extractions called for by U.S.P. and the 4 additional extractions, he then added to the mixture of water and what was left of the tablets, 200 mcgs. of estradiol for the purpose of seeing whether it could be recovered quantitatively for following the U.S.P. procedure and he recovered 97% of the put-in quantity. [R. 61.]

In addition to these analyses they simulated tablets and analyzed these. [R. 62.] They weighed out sugar and added to that a small amount of magnesium stearate and mineral oil, those being the excipients commonly used in preparing tablets of this sort, and added a portion of this mixture which would correspond to an average weight tablet in the samples in question, added to those known amounts of estradiol and then analyzed the

mixture by the U.S.P. assay method. This material was not made up into tablet form. It remained powdered. The excipients used were corn starch, sugar, mineral oil and magnesium stearate. The mixture made up would be the equivalent of 10 tablets. [R. 63.] They used a mixture which would be the equivalent of 10 tablets because the quantity called for in the U.S.P. would be tablets each containing 200 mcgs. of estradiol. The tablets in question were labeled to contain 22 mcgs. of estradiol per tablet. In order to run the U.S.P. analysis, therefore, the equivalent of 9 or 10 of those tablets would be necessary in order to have the equivalent of a tablet containing 200 mcgs. of estradiol. [R. 65.] In connection with this simulation they were able to recover in all cases the amount of estradiol placed in the mixture.

On rebuttal Mr. Carol stated that the first time that an assay of estradiol in tablet form was prescribed in any official compendium was in the U.S.P. XIV, November, 1950, issue [R. 281], and he testified concerning extraction principles upon which the extraction procedure was based having been known for many years. [R. 281-283.] The U.S.P. method says nothing of the actual tablet strength to be analyzed. It merely provides that a weighed number of tablets containing a total of 200 mcgs. shall be used. [R. 283.]

In his work he has analyzed, according to U.S.P. procedure, other tablets containing less than 22 mcgs. per tablet of estradiol and found that they contain, as provided in U.S.P., 90 to 115% of the labeled amount. [R. 284.] He then discussed the various constituents found in the products in question and the effect of the extraction procedure upon them. [R. 284, 285.]

Mr. Carol stated that a competent chemist should be able to make the U.S.P. XIV assay method for alpha estradiol tablets and run an accurate assay in the manner prescribed in that volume. It would not be necessary for such a chemist to have had wide assay experience with such a product. [R. 292.] He does not mean that the U.S.P. method could not be improved upon as he has never seen any method that could not be improved. He only says that the U.S.P. method is the best method possible that he knows of to use for the assay of estradiol. In his analysis he did not precisely follow the U.S.P. method. [R. 293.] He used the infrared procedure which would be at the end of the final reading or estimation. So far as Dr. Banes was concerned, he followed the U.S.P. procedure but deviated from it with regard to some samples. Others he made no deviation in extraction or otherwise. [R. 294.]

Dr. Banes and Mr. Carol's assays differed in the final result to the extent of 1 mcg. each. [R. 295.] If an assay is run several times by competent, qualified chemists and duplication of results are not obtained, and they are learned in the field of analytical chemistry and make no mistakes in any manipulation, and cannot get duplication of results, then it means that either the method of assay is faulty or that the samples with which they start do not have the same composition. The U.S.P. method provides for the spectrophotometer method at the end of the assay for the purpose of reading or determining the amount of estradiol present. [R. 296.] It makes no reference to the use of an infrared method. [R. 297.] He did not analyze any of the 110 mcg. products which were manufactured at the same time that the products in question were manufactured. No samples of the 110

mcg. products were obtained, otherwise they would have gone to him for analysis. [R. 298.] He used the infrared method because it showed the exact amount of estradiol or whatever material is present. [R. 299.] With regard to his testimony that he had conducted some experiments to determine his ability to extract estradiol from excipients into which they had been absorbed, in his experiments they added estradiol to the mixture and then reextracted and obtained 97 or 98% of the amount put in. *The amount of estradiol put in was not 22 mcgs. but was 10 times that or 220 mcgs.* [R. 330, 301.]

(3) An Official Assay Method Is Adopted After the Manufacture and Shipment of the Products in Question.

Volume XIV U.S.P., or the 14th revision, became official November 1, 1950. There appeared in that work for the first time on page 227 the recognition or listing of alpha estradiol tablets and a method for assay for those tablets.

The products involved in Counts I and II were shipped August 22, 1949. Those in Counts III and IV, January 24, 1950. Those in Counts V and VI, April 13, 1950. Those in Counts VII and VIII, July 12, 1949, and those in Counts IX and X May 25, 1950. [See Ex. 1.]

As heretofore mentioned, not only were the shipments involved, and necessarily the manufacture of the products in question prior to and in many cases long prior to the time that an assay method for estradiol tablets became officially recognized, but as well all of the assays of the samples of the products in question, were conducted by the Government witnesses prior to the time that there existed any official method for the assay of estradiol tablets.

(4) The Notice of Alleged Violations to Defendants.

In 1950 a Notice of Hearing was received by Woodard from the Food and Drug Administration in Los Angeles alleging that certain products had been picked up bearing Lot Nos. 497,567 and 897,618 and that upon analysis these products were shown to be below the labeled potency of 22 mcgs. of estradiol per tablet. A hearing before the Food and Drug Administration was had and a couple of months later another Notice of Hearing, followed by a hearing, was had concerning samples of certain products being Lot No. 107,694 being below potency. Following these hearings Woodard contacted a number of laboratories to have samples of the lot numbers involved assayed for the purpose of determining the amount of estradiol present in the tablets. One of these was Adam Laboratories of New York. Others were Bio-Science Laboratories of Los Angeles, Shankman Laboratories of Los Angeles and Truesdail Laboratories of Los Angeles. Samples of tablets involved in the 3 lot numbers were sent to them for assay. [R. 72, 73.] Correspondence passed between the Food and Drug Administration and Woodard as reflected by Exhibit 2 and in a letter dated July 17, 1950, Woodard addressed a letter to that Administration advising them that the variations in the results of the assays conducted by these laboratories had been so great that the assays were meaningless, that the raw material used in the making of these tablets was tested and found up to the necessary potency. The materials and controls used in the manufacturing process were checked and

found to be satisfactory, all of which indicated that the required amount of estradiol, the amount declared on the label to be present in the tablets, were placed in the tablets and the question was raised whether it was possible for the tablets in question to be assayed by any known method and accurate results obtained. Following that letter another letter was addressed to the Food and Drug Administration by Woodard on December 5, 1950 advising of the assays made and the results of these assays received from the several laboratories that had been called upon to conduct them. This information was submitted for the purpose of letting the Food and Drug Administration know the efforts that Woodard had made to find out where the trouble lay. One of these laboratories was Adam Laboratory in New York, and there is included in Exhibit 2 correspondence passing between that laboratory and Woodard. That laboratory was the only one that had found on assay that the samples of the product involved had been equal to or above the declared potency. As a matter of fact, by reason of the results reached counsel for defendants made a trip to New York and took the deposition of Elizabeth Adam Weiss. However, counsel for the defendants stated that he was not going to offer the testimony of Miss Adam concerning the assays conducted by her for the reason that as a result of subsequent examination and investigations in Los Angeles he was satisfied that her conclusions were incorrect. [R. 97.]

(5) Assays of Samples of the Products Are Obtained by Defendant and the Results Thereof.

All of the laboratories retained by Woodard to conduct assays of samples of the products in question, together with the results obtained, are set forth in a letter of December 5, 1950, part of Exhibit 1, to the Food and Drug Administration. It will there be seen that these assay results varied from 2 mcgs. per tablet to 14½ mcgs. per tablet, eliminating, however, the findings of Adam Laboratories.

Dr. C. E. P. Jeffreys, a consulting chemist and holding a Ph.D. degree in chemistry and Technical Director of Truesdail Laboratories, Inc., received his bachelor and master degrees from the University of Texas, and his Ph.D. degree from the California Institute of Technology. He taught at both of those institutions during his graduate study days and has done post-doctorate research at Cal Tech for two years in biological chemistry. [R. 203.] Truesdail Laboratories is a general consulting laboratory employing the analysis of materials. He has been connected with that laboratory for about 15 years and in connection with his work conducts the assay of materials. On July 27, 1950 he received a sample of the product in question from Woodard bearing Lot No. 004,769. The correct Woodard Lot No. of this sample was 107,694, a sample of the products involved in Counts V, VI, IX and X, but Woodard assigned a fictitious lot number (No. 004,769) to that sample sent to Dr. Jeffreys because they had sent out so many other samples of that

lot number for analysis that they decided in order to avoid confusion to give it a fictitious lot number and let the assays start from there. [R. 228.] He was requested to conduct an assay of those tablets for the purpose of determining the amount of estradiol in the tablets. Prior to that time he had been requested by Crest Laboratories to run an assay of similar tablets for estradiol content but did not because he did not feel at that time that there was an acceptable method available for commercial assay of such a tablet. That was prior to the adoption of the U.S.P. method. On or about July 27, 1950 Dr. Jeffreys had received a copy of the U.S.P. XIV which was to become official November 1, 1950 and after having obtained that volume he ran an assay according to the method prescribed in it for estradiol tablets. He took a sufficient number of the tablets to equal 200 mcgs. of estradiol in the test sample, as the U.S.P. method calls for tablets containing 200 mcg. rather than 22 mcg. Due to the low potency of the tablets the amount of excipients made a very bulky mass and he had to increase the relative amount of solvent in order to handle it. The assay results were variable and low. He felt that the difficulty was in the lack of complete extraction of such a small amount of estradiol from the large amount of excipients. Therefore in attempting to improve the efficiency of extraction, instead of grinding the tablets into powder and then wetting them with water, alcohol and acid, the tablets were placed in a Waring blender or mixer and mixed in order to obtain a more intimate mixture of the insoluble material with the solvent, hoping thereby to extract a larger proportion of the estradiol. Even by that procedure low results were obtained, namely 9.5 and 9.1 mcg. per tablet. Mixing by the Waring

blender is not specifically prescribed in U.S.P. procedure but it is a means of getting more intimate contact between the material or excipients which is in large part insolvent and a liquid solvent, in order to more efficiently be able to extract the soluble material—estradiol —from the mixture.

In any assay procedure the first thing necessary is to extract the material that is to be assayed, such as estradiol here, from the other material or the excipients with which it is in combination. The essential thing in any analysis is this separation in such form that it can be measured, separated from all other materials. [R. 205, 206.]

In the science of analytical chemistry such an extraction process is very often a major problem. For instance, as applied to this case where there exists a mixture of soluble and insoluble materials, such as the estradiol which is soluble and the excipients which are not, there is often an adsorption of the soluble material on the surfaces of the insoluble material, holding of the material to be assayed which would ordinarily be soluble in the solvent. In other words, it sticks to the insoluble surfaces. It is essentially an interaction between surfaces, surface versus surface, which is interaction between the molecule that is adsorbed to the solid surface and in some cases it is quite difficult to remove this adsorbed layer by a solvent which would easily dissolve the estradiol, for example, if it were not in combination with these exhibits.

In connection with the product in question labeled to contain 22 mg. of estradiol, if the proportion of estradiol to the excipients present in the tablet was 22 es-

tradiol to 324,000 parts of excipient (which was the ratio of the tablets in question), that ratio would of course have a bearing on the success of the extraction of the estradiol, for the more excipients the more free surface of insoluble material and consequently the more adsorption there would be thereon of estradiol and the amount of estradiol that could be extracted would decrease with the increase of the solid surfaces of excipients which could hold it back. [R. 207.]

In an assay procedure of tablets such as these, he would not be able to know that all of the estradiol had been extracted unless he knew the amount that was put in, and obtained an indication of having gotten the total amount out by the analysis. By following the U.S.P. method in assaying a tablet such as this containing only 22 mcg. per tablet—a microgram being one millionth of a gram—he would not be able to say that all of the estradiol had been extracted. [R. 208.]

It is not possible for a chemist to make a determinative assay of a tablet such as this without having a blank tablet, that is, one containing all of the excipients contained in the tablet subject to question, but with no estradiol in it or with prior knowledge of the excipients in the tablet in question and the quantities. The reason for this is that the object of the assay procedure is to interpret the amount of estradiol at the end of the procedure simply on the basis of how much light the solution being investigated happens to absorb. In such a procedure one is depending upon the success of the prior operations to have removed everything except the estradiol from the excipients and have it in the final solution. [R. 211.] With a blank tablet it would be possible to know

by the assay method the interferences of the excipients and in the assay of the tablet itself with the estradiol in it corrections could be made for those interferences.

The U.S.P. method is a very sensitive method but it is cumbersome and depending upon the amount of the excipients in the tablet it may not be efficient, and the greater the disproportion between the active material—estradiol—and the excipients, the less efficient the method is likely to be. [R. 212.] In using the U.S.P. method it is possible for material to be extracted along with the estradiol and on the final reading of course the result would not be accurate and even with a high result as might be expected under those circumstances, it would not be indicative of any significance and even with such a result it would not be possible to know that some of the estradiol had not remained with or been adsorbed by or on the excipients.

The Kober method of assay does not contemplate or provide for the assay of estradiol tablets as distinguished from estradiol alone. It is simply an assay method for pure estradiol and does not provide for the extraction of estradiol from any excipients. [R. 213.] If one were to use that method they would have to use some procedure for extracting the estradiol first and it applies only to the final reading and measurement of the material. The most difficult job in any analytical chemist's experience is the separation of the ingredient to be measured into a measurable form. The actual measuring is usually quite simple. [R. 214.]

In the assay conducted by him of the tablets in question in his opinion he did not extract all of the estradiol present and this because of the large disproportion be-

tween the estradiol and the excipients. In his opinion the enormous amount of excipients, partly soluble and partly insoluble, that a complex organic compound with active bond such as estradiol has, in all probability adsorbed on portions of the excipients or was left behind and was not gotten out for the final measurement process. He said this for the reason that from general experience with the difficulties of extraction of materials even the simple extraction of inorganic materials it is a difficulty always present. Extraction procedures are the last resort of American chemists and they are avoided whenever possible. They are realized to be relatively inefficient. The phenomenon of adsorption is always a difficult thing to handle. For example, assume that estradiol is mixed with talc. No matter how many times it may be washed with something that would dissolve estradiol, there may still be estradiol on the talc and there is an equilibrium each time you wash it between what is on the surface and what is taken off. After taking off a certain proportion relative to the amount of effective adsorbing surface, the amount that can be taken off by subsequent extractions becomes smaller. [R. 215.]

In his opinion the U.S.P. method for the assay of an estradiol tablet is not applicable or suitable to or accurate for the assay of the tablets involved in this case because the potency, the amount of estradiol relative to the amount of excipients is too disproportionate for the method to be effective. [R. 215.] The conduct of an assay is the employment of analytical chemistry which teaches to effect the separation of constituents of mixtures and enables one to estimate quantities by some means after the unknown materials have been separated into pure components in a case like this. A competent

chemist should be able to take an assay procedure as set forth in U.S.P., use it for the first time and do it accurately if the method is any good. [R. 216.]

U.S.P. is an official compendium or standard of so-called official drugs and assay procedures are given to enable chemists and pharmacists to determine whether any batch of drug material meets the specifications of U.S.P. A competent, qualified chemist should have no trouble in pursuing this method. [R. 216.]

The Truesdail Laboratories is frequently called upon to conduct U.S.P. assays of products which they had not assayed before. This happens very frequently and is not at all uncommon. [R. 217.]

If some of the excipients have been extracted along with the estradiol not necessarily a higher reading on the final estimation will result. If the chemical material or excipient extracted with the estradiol at the time of reading absorbs light, it will give a higher reading but not otherwise and in some cases interfering materials will prevent the proper color development on the final estimation. [R. 220.]

At no time did he know what the excipients in the tablets were. He was furnished with no blank material. [R. 221.] His conclusion that the low result obtained by his assay was due to inapplicability of the U.S.P procedure to this tablet, was based upon his experience with such method of extraction procedures and he was not retained to test the efficiency of the U.S.P. method but instead to assay the product according to that method. [R. 223.] In any assay procedures run by him the tests are run in duplicate and in this connection the duplicate results did not agree at all. This was when they ran

the assay strictly according to the U.S.P. method and any method of assay is not an accurate one if duplication of results cannot be obtained. Explaining this he stated that in any assay, particularly in organic analysis, there is going to be certain variability of results—just unavoidable variability. Even the U.S.P. method allows a variation from 90 to 115% in the assay of estradiol tablets. The difficulty with organic materials is that the allowable limits of error are somewhat looser than for instance in analyzing a piece of steel for its constituents, but when assaying a material of the kind in question and one of the assays shows 20% as against 80% for the other, or something like that, then definitely something is wrong and the results are no good and that was comparable with the results obtained at the first when the U.S.P. method was run exactly as it is set forth. [R. 224, 225.]

In answer to some questions by the Court, Dr. Jeffreys stated that with reference to the test conducted by him wherein the Waring blender was used and he recovered for final estimation 9:5 mcg. of estradiol, that 12½ mcg. remained in the residue and couldn't be extracted and the 12½ mcg. is an extremely minute amount. If the tablet in question had been a U.S.P. tablet containing 200 mcg. of estradiol and 12½ mcgs. remained with the excipient, the percentage of loss would be quite small, but when tablets containing 22 mcg. such as these in question are assayed and 12½ mcg. remained unextracted, the percentage is very high. He knows of no method that he would want to depend upon as an accurate assay for determining the amount of estradiol present in the tablet when the amount alleged to be present was only 22 mcg. [R. 226, 227.]

Don Carlos Atkins, employed by Crest Laboratories as Director of Laboratories since July, 1950, received his Bachelor and Master's degrees in chemistry at U.C.L.A and has been working on his Ph.D. at U.S.C. He is a member of the American Chemical Society, the Sigma Phi and Phi Lambda Epsilon Societies and the Academy for the Advancement of Sciences. He received the Morrison all-Navy scholarship for his undergraduate work at U.C.L.A. [R. 157.]

Immediately prior to coming with Crest Laboratories he was at the University of Southern California working on his Doctor's degree.

He examined the work sheet, Exhibit B, which was the work sheet used in the manufacture of the products involved in Counts I, II, VII and VIII, being Woodard Lot No. 497,567, and Crest control No. 2571, and he stated that the ratio of the amount of estradiol present in a tablet to the amount of excipients in the same tablet called for by that work sheet was approximately 22 parts of estradiol to 324,000 parts of excipients. [R. 158.] In the assay of estradiol at Crest Laboratories they had run a number of tests using various published methods for assay of that product. They have examined those procedures and evaluated them according to their own opinion, including the U.S.P. XIV method. He has conducted approximately 100 assays of estradiol tablets. He was then asked, with reference to the U.S.P. method, and keeping in mind the excipients present in these tablets, which of those excipients in his opinion could interfere with the readings or final estimation of the amount of estradiol in the tablets at the end of the procedure. This question was subject to objection

on the grounds that merely conducting 100 assays did not qualify the witness to answer the question. The Court overruled the objection, stating that the objection went to the weight of the testimony rather than to admissibility. [R. 159, 160.] He had used a colorimeter for the purpose of finally estimating the quantity of material at the end of an assay over 1,000 times. One of the constituents that would interfere with the final readings would be mineral oil and others would be starch, sterotex and possibly sugar, and those excipients were present in the tablets here. They could interfere in several ways which he mentioned. [R. 160.] He heard the testimony of the simulated product made up for experimental purposes by the Government witnesses. The Government used magnesium stearate in its simulated product and that is not involved in the present tablet. It would probably be used as a substitute for sterotex and in his opinion it would be soluble to a greater extent than would the sterotex and thus tend to interfere with the proper conduct of the assay. [R. 161.]

The degree of solubility would affect the instrumental reading at the end of the assay.

There are 2 steps in the U.S.P. XIV procedure, One is to extract the estradiol from the excipients and the other is to determine the amount of estradiol extracted by the use of a colorimeter or some other machine. The U.S.P. method is a long method—long in the number of steps to be taken before one can make any attempt to determine the amount of estradiol extracted. [R. 162.] Magnesium stearate being more soluble in chloroform, the extracting material would tend to remain with the residue that was supposed to contain nothing but es-

tradiol and would thus interfere with the final readings. [R. 163.] It might give a higher reading depending upon the adsorption of light by magnesium stearate but even if a higher reading were obtained it would not necessarily mean that all of the estradiol had been extracted. He has examined the Kober method of assay and that method does not give the information necessary to conduct an assay of a tablet such as this because it provides for the analysis of pure estradiol alone and not in combination with anything else. [R. 164.] That method is useful where one has a liquid material that purports to be estradiol but it is desired to run an assay to be sure whether it is and, if so, how much but it provides no method for extraction of estradiol in combination with solid excipients such as were present here.

The extraction procedure is one of the principal steps in the assay of estradiol because if all of it is not extracted then obviously the amount of estradiol in the tablet itself cannot properly be measured at the end of the assay. [R. 165.]

The purpose of the excipients is to give a tablet the desired weight, shape and form and to enable a person to consume the finished product, as it would be very difficult to take estradiol in its pure form.

He was aware of no method appearing in the scientific literature prior to the time that the U.S.P. method became official, November 1, 1950, designed for the assay of tablets containing estradiol in combination with other excipients. [R. 166.] In any analysis in which there are other ingredients than the one to be measured, those other ingredients may affect the analysis and therefore any complete assay must take into account the excipients

present. If each one is not taken into account in the assay procedure, the analyst is not absolutely certain whether all of the estradiol has been extracted or whether something has been extracted along with the estradiol which interferes one way or another in the final estimation. [R. 167.] In connection with the tablets in question, it was his opinion that there were excipients present which tended to interfere with the assay. In his opinion the principal one was mineral oil. Explaining this he stated that in the assay it is necessary to determine the amount of estradiol at the end of the assay by measuring the absorption of light which is passed through a solution containing the estradiol and this absorption is proportional to the amount of estradiol present. If, however, there is some other material in this solution that is being estimated which also absorbs light, it will interfere with the true reading of the amount of estradiol present and in his opinion that happens in the analysis of these tablets.

He had conducted experiments for the purpose of determining whether there were excipients that interefered with the assay. In connection with that experiment he made up some tablets identical in every respect with the ones in question, with the mineral oil and sterotex left out. In such cases the tablet assayed up to the claimed potency. He felt that the U.S.P. procedure was not satisfactory for the assay of these tablets because every time he ran the U.S.P. procedure he found an interference which indicated a higher quantity of estradiol in the tablet than he knew to be present. [R. 169.] In this connection he made up a batch of tablets containing all of the excipients and in the same amounts as those involved here. They were assayed according to the U.S.P.

procedure and he found in the final estimation 97 mcg. of estradiol, whereas he had only put in 23. Continuing, then, he made a modified procedure by which the estradiol is extracted by a continuous extraction device—the Soxhlet device—mentioned previously and the extraction fluid used was ether. This ether extraction of estradiol was evaporated down to dryness in a steam bed under nitrogen atmosphere and the residue taken off immediately in ethanol. To this was added sulphuric acid which develops the color. From the density of this color, which is developed because of the addition of the acid, and subsequent treatment of the solution, one can determine the amount of estradiol present. This is an improvement over the U.S.P. method because the multitude of extractions with the great deal of handling involved in the U.S.P. procedure is eliminated but even with that modified procedure there was still interference if mineral oil was present in the mixture.

He then conducted an experiment using the same excipients in the same amount as those present here but with the mineral oil alone omitted. In this he followed his modified procedure and obtained very good results, that is to say he put in 73 mcg. of estradiol and recovered on the final estimation 68.5. As a result of those experiments and his work it is his opinion that the presence of excipients makes it necessary that an analysis of estradiol be made with full knowledge of the exact excipients in the tablet as well as their amounts and if that is not done a correct assay cannot be obtained. [R. 172.]

In any assay procedure the margin of error increases as the potency of a product decreases. For example, if one added 100 mgs. of a certain material and there was

left in the assay procedure 1 mg., the error would be about 1% but on the other hand if one were analyzing a product containing 2 mgs. and 1 mg. were lost, the loss would be 50%.

Considering the ratio of estradiol in the tablet to be 22 of estradiol to 324,000 of excipients, that ratio would definitely affect an assay result, for one is analyzing to determine the presence of a very small amount of material in a large amount of excipients, which means that the assay procedure must be such as to pick out that particular material that is being assayed and must state quantitively how much of it is present and the probability of extracting it all is not as great as it would be if there were more estradiol present or the ratio between the amount of estradiol and the excipients less. In other words, in this procedure with these tablets what is attempted is to pick out 22 parts from a mass of 324,000. [R. 174, 175.]

It is his opinion, therefore, that the U.S.P. XIV assay procedure is not suitable or accurate for the assay of a tablet such as this containing but 22 mcg. of estradiol in combination with a great mass of excipients. [R. 179.]

He had made no assay of the tablets involved in the counts subject of the Information. [R. 180.]

Anything that is soluble in the chloroform, which the U.S.P. method calls for, would stay with the estradiol and be measured in the final estimation. [R. 183.] If the excipients are not completely removed in the extraction procedure they will interfere with the final read-

ings and it is his opinion that they are not removed completely in the U.S.P. procedure. He would not be prepared to say whether the reading would be higher or lower if the sterotex and mineral oil remained in the solution with the estradiol. It is his opinion that the U.S.P. procedure in itself does not permit one to make a conclusion because sometimes a higher result is obtained and sometimes a low result is obtained in the U.S.P. procedure, depending upon the amount of excipients. [R. 185.]

In his opinion if these excipients remained in the solution with the estradiol they would give a higher reading and not a lower reading. [R. 186, 187.]

He was then questioned extensively on cross-examination concerning the number of steps and what was done in the U.S.P. procedure [R. 187-190] and then the Court said,

> "Of course, gentlemen, if you are going to come out with 10 or 12 (steps) I can't see the materiality. I frankly can't see the materiality of this questioning." [R. 190.]

Counsel then stated,

> "The whole purport of the questioning was to show simply that while it is contended on the one hand that the manufacturing process cannot possibly result in any loss and does not, yet because there are 12 steps in the analysis, in that analysis you get all sorts of possibility of error in loss. It was simply that point I was trying to develop."

To which the Court replied,

> "Well, counsel, if as you think on these steps in the manufacture the responsibility still rests with the manufacturer * * * at the end of which are 5 or 10 steps when he gets through to have the required amount of estradiol in it, what difference does it make whether it takes 1,000 steps or 5 steps." [R. 191.]

Sterotex is more soluble in chloroform than magnesium stearate and would tend to interfere with the reading. He has not measured the interference of sterotex itself but in his opinion the interference of all excipients would tend to give higher readings and being more soluble would likely be found in the final result, more so than magnesium stearate. [R. 192.]

The mineral oil definitely interfered with the assay and gave a cloudy solution in the end. There should be no more than three things in the product which would give a cloudy mixture if the separation of the solutions had been complete and those would be mineral oil, sterotex and estradiol. [R. 193.] They shook the mixture four times and still got the same cloudy result and the cloudy mixture gave a high reading. In analytical chemistry the chemist learns a variety of extraction procedures which can be adapted to a particular product subject of analysis, provided the extraction procedure is applicable to that type of product and if he is to get a definitive answer and there is a possibility of interfering materials, he must know what extraction procedure should be used. [R. 195.]

Answering questions of the Court Mr. Atkins stated that in his experiment he used 23 mcgs. of estradiol and on the final reading it showed 96, which he attributes to the interference of the other excipients in the tablet, principally mineral oil and sterotex. If a person put in 23 mcgs. and obtained a final reading of 15, it would appear that he had successfully avoided interference with the reading but it would not mean that the interference in the sense of incomplete extraction of the estradiol from the excipients had been avoided. Even though a value of 96 mcgs. were obtained on the final reading, it would not mean that all of the estradiol was extracted. He did not know and it would be impossible to know whether the 96 mcgs. of apparent estradiol was 90% estradiol and 10% interfering material, or the other way around. [R. 197.]

With the mineral oil and sterotex in the product they dissolve with the estradiol and are confused with the final reading but he is not able to say whether or not, along with the mineral oil and sterotex all of the estradiol was extracted. [R. 199.]

If some other chemist conducted an experiment and came out with less estradiol than Atkins did, that is with tablets containing sterotex and mineral oil, he did something different than provided for in the U.S.P. procedure, which was the one that Atkins followed and in thus avoiding the interference encountered by Mr. Atkins he did something different than that prescribed in the U.S.P. procedure. If he followed it and came out with less he was apparently able to avoid the interference. [R. 202.]

(6) Experimental Assays Are Caused to Be Made by Defendants and the Results.

Mr. Galindo, Vice President and Production Manager of Crest Laboratories, stated that at the request of counsel for the defendants on June 27, 1951, he had prepared a work sheet for the manufacture of about 7,000 tablets each containing 22 mcgs. of estradiol. The work sheet was prepared identically with the work sheets pertaining to the products in question, Exhibits B, C and D, and that work sheet was offered into evidence as Exhibit H. At this time an objection was raised to the introduction of Exhibit H on the grounds that the proof sought to be made was some time after the manufacture of the tablets in question and that Exhibit H did not involve any of the shipments involved in the case and it therefore had no probative value. This objection was argued extensively and counsel for the defendants stated that after returning from New York and the taking of the depositions in that city, in order to test or determine whether 22 mcgs. of estradiol could be extracted by the U.S.P. method from tablets composed such as these, he arranged for an experiment to be made wherein blank tablets composed exactly as those in question would be prepared identically with those in question and then the amount of estradiol in question, or the equivalent, would be put into the tablet and this assay run. This objection was sustained, the Court stating that even so such testimony would not be admissible. This matter was argued at considerable length, the court stating that he was not interested in any test made at a later time and of some experimental tablet even though composed in the same way as these and counsel for defendants then found it necessary to make an offer of proof, which he did. An

objection was made to the offer of proof and the objection sustained. Counsel for the Government however withdrew his objection and the testimony continued. [R. 115-126.]

The work sheet of these test tablets was made up identically with those involved in this action, the same amount of estradiol, the same amount of excipients, and so on. [R. 127.]

In the manufacture of this batch of tablets, Mr. Galindo, Mr. Atkins and the pharmacist at Crest Laboratories personally followed each step throughout the course of the entire manufacture until the finished product was obtained.

On the same day, using the same work sheet, they made up another batch of tablets with the same ingredients in the same amount but with the estradiol omitted, and this batch was manufactured in precisely the same way, with the same men personally supervising each step in the manufacture.

Both batches were completed June 27, 1951 and samples of both sent to Dr. Robert E. Hoyt at the Cedars of Lebanon Hospital in Los Angeles. [R. 128, 129.]

The experiment which follows was conducted by Dr. Robert E. Hoyt in conjunction with Dr. Harry Sobel, both of the Cedars of Lebanon Hospital, and their experiment involved the use of samples of the experimental batch testified to by Mr. Galindo, prepared from the work sheet, Exhibit H, and manufactured with the same ingredients in the same proportions and with the same amount of estradiol as concerned the manufacture of the products in question. Their experiment also involved the

use of the placebo or blank tablets testified to by Mr. Galindo, manufactured in precisely the same way but with the estradiol omitted.

Dr. Robert E. Hoyt is employed in the Division of Laboratories, Cedars of Lebanon Hospital. [R. 229.] He obtained his B. S. degree at the University of Washington in 1933; M. S. degree, University of Minnesota, 1934; Ph. D. degree, same university, 1939. His major was bacteriology, urinology and pathology. His academic positions were as follows: Teaching fellow and subsequently instructor University of Minnesota Medical School [R. 230], Instructor School of Medicine University of Utah, Department of Bacteriology and Pathology about 1942; then co-director Institute of Experimental Medicine, College of Medical Evangelists, Los Angeles. The principal function of the Institute was to carry out experimental studies in medicine and related fields and to perform or supervise performance of various laboratory procedures considered too delicate or difficult for the average laboratory personnel to carry out properly. [R. 231, 232.]

An important part of their procedure was the conducting of assays of materials from time to time. These included assays for various steroid hormones of the sex hormone and adrenal cortex type excreted in different proportions and under different conditions, with various dose proportions. They carried out determinations of such particular substances in various body fluids and tissues of patients, including estrogenic and urinogenic hormones and adrenal cortex hormones of that sort. [R. 232.] He was associate professor, Department of Bacteriology at the College of Medical Evangelists. After leaving there he spent a year in Salt Lake City where he was bio-chem-

ist with the Veterans Administration and Assistant Clinical Professor, Department of Pathology. In addition to his present position at Cedars of Lebanon, he is assistant clinical Professor, Department of Infectious Diseases, U. C. L. A. During the war he lectured at the U. S. C. Medical School in the Department of Bacteriology. [R. 233.] He has written and published about 35 papers dealing with scientific subjects. One of these had to do with the development and evaluation of an assay procedure for pregnandiol appearing in the urine of pregnant women, which is a field related to the subject of estradiol, since the drugs are structurally related, behave similarly, and the problems of extraction and evaluation are roughly the same. This paper was prepared in conjunction with Dr. Raymond Mitchell [R. 233, 234] and it appeared in the Journal of Clinical Endocrinology in February, 1950. [R. 234.]

In the middle part of 1951 he received some tablets from Crest Laboratories. They were two large bottles containing tablets, one labeled "placebo tablets" and the other gave a serial number and stated that the tablets contained 23.3 mcgs. of estradiol per tablet. A placebo tablet is one which does not contain the item which is subject of investigation—a blank tablet. [R. 235.] Their problem was to determine whether there might be some difficulty involved in the extraction of estradiol from the tablets which would cause the final result to be erroneous. Dr. Hoyt had made up a chart showing the results of the assay procedures conducted by him which was introduced

into evidence for illustrative purposes as Defendant's Exhibit I. [R. 248.]

Referring now to Exhibit I, with respect to the first horizontal column "Standard 200 mcg.," the figures in that column mean this: They took a sample of pure estradiol without any excipients in the amount of 20 mcgs. and made readings of this pure material on the colorimeter with the results indicated in that column. The reason for so testing the pure material was that if the liquid amounting to 20 mcgs. of estradiol was placed in the top of a separatory funnel and drawn out, 20 mcgs. would not be extracted from the bottom because some is going to cling to the walls of the vessel and though it be rinsed and washed one cannot be perfectly certain that it will all be gotten out as there is inevitably a loss when a fluid is transferred from one funnel to another. The U.S.P. method provides for a correction for a presumed loss, that is, a standard solution containing a small amount of pure estradiol is processed by going through all of the steps identical with the sample to be tested and this standard is considered to compensate for handling losses and for solubility losses which will occur as it is placed from one solvent to another.

So the second horizontal column describes the results obtained when the pure estradiol was processed throughout the U.S.P. method. [R. 238, 239.] It was their first problem to discover how much of the pure estradiol could be extracted without the presence of the excipients in following the U.S.P. procedure. Therefore, following

the second horizontal column over to the 4th vertical column, they found that instead of 20 mcgs. of estradiol recovered there was 14.5 mcgs. recovered, or a recovery of 72.5% and that was then used as the basis for a correction factor in testing the tablets themselves. It is an amount of loss to be anticipated to occur in the method itself. [R. 240, 241.] (The first horizontal column represents the color standard and shows what color will be developed by 20 mcgs. of pure estradiol. [R. 242.]) 72.5% of the total amount put in being recovered, meant a loss of 27½% of the pure estradiol when assayed without anything else according to the U.S.P. procedure. [R. 242, 243.]

The third horizontal column represents a test as follows: With the tablets containing serial No. 2571-B and labeled to contain 23 mcgs. when run through the U.S.P. test it was found, as shown by the 4th vertical column, that 10.1 mcgs. of the 23 were recovered or, as shown by the 5th vertical column, 44% of the labeled potency was recovered. After making the correction for the known loss of 27½%, this represented a recovery of 13.8 mcgs. instead of 23, or 60% of the total labeled potency. In other words, 40% of the labeled amount was lost somewhere in the assay procedure after making correction for the amount that it was known would be lost. [R. 243, 245.]

Then coming to the fourth horizontal column the figures there represented a test conducted as follows: Dr. Hoyt was then faced either with the proposition that the tablets

labeled to contain 23 mcgs. did not contain that amount or that the extraction of the estradiol had been incomplete. In order to test that, they ground up tablets, the placebo tablets, stated to be of the same composition as the previous lot with the exception of the estradiol being omitted, and to those ground up tablets he added a specific known amount of estradiol, 20 mcgs. to the material. 20 mcgs. was selected instead of 22 because the standard solution is made up to 200 mcgs. and that figure was selected purely as a matter of convenience. He might just as well have taken 30 or 15. It was a figure selected as being easily measured and approximating the 23. [R. 245.] Referring again to Exhibit I by following the U.S.P. procedure in the test of the placebo tablets, as shown by the fourth column, 10.1 mcgs. of estradiol were recovered or 50% of the amount originally put in. After correcting for the known loss of 27½% the mcgs. recovered amounted to 13.8 mcgs. instead of 20, or 69%, meaning a loss of 31% estradiol which could not be accounted for and it was his conclusion that all of the estradiol was not recoverable when held in excipients of the sort found in those tablets when following the U.S.P. method.

The last horizontal column represents an attempt to demonstrate the presence of more estradiol than was possible under the U.S.P. method. In that test he ground the tablets containing the estradiol, some of the same tablets tested in the test represented by the third horizontal column. He ground sufficient tablets to contain 233 mcgs. A sample of 23 mcgs. was then used, placed in a Soxhlet extracting device and extracted continuously with ether for 12 to 18 hours. The ether extraction was processed and the color developed and it was shown that 16.4 mcgs. was recovered as shown by the 4th vertical column, or

71.2% recovered. They were not retained to devise an assay method but simply to utilize the one at hand and they did not calculate the inherent loss though there would be such a loss. The 16.4 mcgs. recovered represented the minimum amount of estradiol which could possibly be present. Even without correction, by using that type of extraction, he was able to recover more estradiol from the tablets than under the U.S.P. method after correcting for loss under the latter method. Therefore it was his conclusion, based upon the assays conducted, that some factor or factors in connection with that test prevented recovery of the estradiol quantitatively. [R. 245-247.] His conclusions would not have been any different had the tablet been 22 mcgs. The deviation would be insignificant. In his opinion it is possible for a tablet such as the ones involved in this case to contain the labeled potency of 22 mcgs. and still on U.S.P. assay show materially less because something in the excipient prevents the estradiol from being extracted. He has not investigated the cause of the difference but in his opinion it would be due to extraction procedure rather than the subsequent purification. When a tablet of this sort contains a good deal of insoluble material, is shaken with a mixture of chloroform and water, there will be variable amounts of emulsions present. This emulsion will vary depending on how briskly the separators are shaken and the emulsion contains both chloroform and water in addition to the inert particulate matter around which it is built. It may be presumed that the chloroform present in the emulsion has extracted estradiol the same as the other chloroform has before the emulsified layer is allowed to break, but it is very difficult for these emul-

sions to break completely when there is so much extraneous material present. Therefore any estradiol that remains in the emulsion will be discarded and will not appear in the final assays. Then also is the problem of the estradiol being dissolved on the surfaces of some of the small particles of insoluble material, the excipients, which is a very important factor. [R. 248-251.] The estradiol that he used in the test and which was put into the placebo tablets was received from Crest Laboratories and labeled "Estradiol—U.S.P." [R. 252.] These tests were conducted at the Cedars of Lebanon Laboratories. Dr. Hoyt and his associate, Dr. Sobel, ran the tests together, 3 in all, each running a test and then comparing results. [R. 253, 254.] The 3 tests were in substantial agreement with each other. [R. 255.] They did not check back on the residue to see whether there was any estradiol left. They simply ran the test according to the U.S.P. method which does not provide for such tests of the residue. [R. 256.] They were dealing with the U.S.P. method and they followed it rather than some other method and the U.S.P. method is not one that he would select if he were interested in assaying estradiol. [R. 257.] In analytical chemistry it is true that chemists adopt particular extraction procedures to the particular substances they are dealing with depending on the quantity and the amount of substances to be analyzed, but when a particular method of assay is prescribed and to be followed, then that method alone is followed without deviation. [R. 258.] He made no investigation as to why some of the estradiol was unextractable. He simply demonstrated that it occurred when the U.S.P. method was followed. [R. 258.]

With regard to the placebo tablets to which he added the estradiol [see 4th horizontal column, Ex. I] the ex-

cipients in the tablet accounted for 23½% loss of estradiol in addition to 27½% that they knew was going to be lost as demonstrated by tests referred to in horizontal column No. 2. [R. 259.] The reason that they did not check back or assay the residue to determine whether any estradiol was left in it was because it did not seem to him that that was part of the problem. The question was whether the U.S.P. method accurately revealed the amount of estradiol present. To devise a new method different than the U.S.P. method was a different problem which did not appear to him to be material. [R. 260, 261.]

The U.S.P. method does compensate for a loss in assay procedure of pure estradiol with the excipients but it does not account for any loss which would be peculiar to the product—the finished tablet itself—and there is no reason why a competent chemist should not be able to follow an assay procedure which is written out and do so accurately providing the method is suitable to the assay of a product at hand. He made no studies as to the presence or the disappearance of any particular excipient in following the test. The one thing that they considered was whether they got back all of the estradiol they added and they found that they did not. If excipients were present in the substance which was to be read at the end of the assay they would not, generally speaking, make the readings higher. The U.S.P. method does provide for a correction factor but from the tests and experiments made by him he was convinced that this fact is far from an established phenomenon. [R. 262.]

Answering questions of the Court he stated that he thinks that there are methods which could be applied to a 22 mcg. product and an assay accordingly be done. He would not say exactly how it could be done. They did

demonstrate that they could recover more by another method, that shown on Exhibit I in the 5th horizontal column, than could be recovered by following the U.S.P. method. He did not assay the actual tablets involved in the litigation. Had they been submitted to him he thinks an analysis or assay could have been made to determine the exact amount of estradiol. Perhaps this would be a biological assay. He is sure it could be done. [R. 263.] By biological assay he means injecting some of the material into an animal to determine the response. This is a very sensitive test but has a greater error with a dissolvable liquid. [R. 264.]

Dr. Harry Sobel, head of the Department of Biochemistry, Cedars of Lebanon Hospital, testified as follows [R. 264]:

B. A. degree in chemistry 1938, Temple University; M. S. degree in organic chemistry, University of Pa. 1940; Ph. D. degree in Bio-chemistry, McGill University, Montreal, Canada, 1946; Research Assistant, Abbott Laboratories, Philadelphia 2½ years; Assistant Chemist in charge clinical chemistry laboratory, Jewish Hospital, Brooklyn; lectured in bio-chemistry McGill University, 3 years; head Baird Foundation Fellowship, Cornell Medical College, New York, where he spent a year [R. 265]; associate on the Donnor Foundation Grant for a year and a half; at Beth Israel Hospital, New York; has been at Cedars of Lebanon in his present capacity for nearly 3 years. His major interests have been steroids, endocrinology and clinical chemistry. Steroids refer to a group

of compounds which go into the making of certain hormones and steroids.

He has written 13 scientific papers, 8 of which directly or indirectly have to do with the subject of steroids, estrogen or estradiol. [R. 266.] The assays testified to by Dr. Hoyt were all performed by Dr. Hoyt and himself. If he were asked the same questions as Dr. Hoyt his answers would be substantially the same. However, he could expand on some. [R. 267.] In his opinion the U.S.P. method should not be described as one to assay alpha estradiol because with that procedure as found in U.S.P., estrone, and particularly estrol, could be determined and mistaken for alpha estradiol. Estrol is removed by the U.S.P. procedure so the designation of the U.S.P. procedure as one for the determination of alpha estradiol is incorrect. There are 3 sources of loss in determining alpha estradiol in the U.S.P. procedure. [R. 268.] There will be a small amount of loss due to the seepage of chloroform through the stop cock at the bottom of the separatory funnel. [R. 269.] There will be a small amount of material unextracted in the aqueous phase of the test. If there is a substance one is partitioning between two phases, like water and chloroform, a certain partition ratio will be set up. This ratio will be maintained so that there will always be something remaining behind and this is another source of loss.

Next in one stage of the assay an alkaline solution is extracted. Here the column is subject to very rapid destruction and alkaline solutions of alpha estradiol are

very easily oxidized and if followed for any length of time will be destroyed. This is another source of loss. Ultra violet rays will attach alpha estradiol, dissolve it and cause additional destruction of it and this is another source of loss. Therefore it is not at all surprising if only 72½% of the pure estradiol could be recovered through the U.S.P. method. In fact that amount of recovery is very satisfactory. [R. 270.] The U.S.P. procedure recognizes a loss and therefore requires the standard solution such as shown by the 2nd horizontal column on Exhibit I to be carried out. In the case of assaying the tablet there is an emulsion formed that does not occur when the pure standard is assayed. [R. 270.] Though the U.S.P. procedure provides for 4 extractions in the assay of the tablet, it is still very likely that a certain amount of the excipient material is entrained in the emulsion. Experiments conducted by him in the past with similar material showed that that happened. Therefore the emulsion seriously interferes with the extraction of alpha estradiol. [R. 271.] This tablet, among other things, contains starch. Starch may absorb itself into some of the material and not be extracted with the chloroform. Techniques established in the past which Dr. Sobel described show this to be a fact. [R. 272.] This explanation was given by Dr. Sobel. [R. 272-274.]

In the final analysis, therefore, there are two sources of loss of alpha estradiol which are not compensated for in the U.S.P. method. Those two methods are the emulsion and absorption. [R. 274.] With a tablet containing

between 100 and 200 gamma of estradiol and assuming a certain loss would take place in extracting estradiol from such a tablet, if simply 5 or 6 gamma were lost it would play no role in the final determination, but in the case of a tablet containing but 23 gammas, for example, such as the tablets involved here, a loss of 6 gamma by virtue of emulsion and absorption become appreciable. It is therefore in his opinion possible for a tablet such as the one involved here to contain 22 mcg. of alpha estradiol and still by following the U.S.P. procedure show materially less. [R. 275.]

He conducted no experiments to determine actually that the losses occurred which he testified about but it is his opinion, based upon his experience, that such a loss occurred. [R. 275, 276.] However, he does know, as shown by Defendants' Exhibit I in the 4th horizontal column, that when they took a placebo tablet and added 20 mcgs. of alpha estradiol there was lost in the procedure 31% of the estradiol after correcting for the amount that they knew they were going to lose of 27½%, which they demonstrated by the test shown in horizontal column No. 2. [R. 276.] In any work that he has done with estrogen it has been absolutely imperative to avoid contact with alkali for any length of time and alkali is involved in the U.S.P. procedure. [R. 278.]

ESTRADIOL TABLETS.

Tabellæ Estradiolis.

Estradiol Tablets contain not less than 90 per cent and not more than 115 per cent of the labeled amount of $C_{18}H_{24}O_2$.

LIMIT OF BETA-ESTRADIOL—Proceed as directed in the test for *Limit of beta-estradiol* under *Estradiol,* page 225, but use aliquots of the benzene solutions prepared in the *Assay* below, each equivalent to 20 micrograms of estradiol.

WEIGHT VARIATION—Estradiol Tablets meet the requirements of the *Weight Variation Test for Tablets,* page 799.

ASSAY—Weigh a counted number of not less than 20 Estradiol Tablets, and reduce them to a fine powder without appreciable loss. Weigh accurately a portion of the powdered tablets, equivalent to 0.2 mg. of estradiol, and transfer to a 125-cc. separator containing 25 cc. of water, 1 cc. of alcohol, and 5 cc. of diluted sulfuric acid.

Dissolve 10 mg. of U. S. P. Estradiol Reference Standard in alcohol to make exactly 50 cc. Transfer exactly 1 cc. of the solution to a 125-cc. separator containing 25 cc. of water and 5 cc. of diluted sulfuric acid.

Treat each of the above aliquots in an identical manner as follows: Extract solution with four 20-cc. portions of chloroform. Evaporate the combined chloroform extracts to about 5 cc., add about 25 cc. of petroleum ben-

zin, and transfer the solution to a 125-cc. separator with the aid of several small portions of petroleum benzin. Add 10 cc. of sodium hydroxide solution (1 in 10), shake vigorously for 2 minutes, and allow to separate completely. Transfer the water layer to a second 125-cc. separator containing 5 cc. of carbon tetrachloride, avoiding transfer of any insoluble matter at the interface. Repeat the extraction with two additional 10-cc. portions of the sodium hydroxide solution, and discard the petroleum benzin layer. Shake the alkaline solution vigorously with the carbon tetrachloride and allow to separate. Draw off the carbon tetrachloride layer into another separator, and wash it with 5 cc. of the sodium hydroxide solution. Discard the carbon tetrachloride, and add the alkaline wash to the main sodium hydroxide extract. Complete the alkaline extractions promptly. Render the combined alkaline solutions acid to litmus paper by the addition of dilute sulfuric acid (1 in 2), cool, and shake vigorously with 20 cc. of benzene. Redistil the benzene to be used if the residue from 5 cc. produces a turbidity with the iron-phenol reagent. Transfer the water layer to another separator, and extract with a second 20-cc. portion of benzene. Wash the benzene solutions in the two separators, successively, with two 5-cc. portions of sodium carbonate T. S. and two 5-cc. portions of water, drawing off the last wash as closely as possible. Drain the first benzene extract into a dry 100-cc. beaker, sprinkle into it about 1 Gm. of anhydrous sodium sulfate, and swirl until the benzene is entirely

clear. Decant the benzene into a 50-cc. volumetric flask avoiding transfer of any of the sodium sulfate. Rinse the first separator with the second benzene extract, clarify the benzene over the sodium sulfate, and add to the flask. Wash the separators and the beaker with two 4-cc. portions of benzene, add the clarified washes to the flask, and add benzene to make exactly 50cc. In the benzene extractions a slight turbidity persisting after 5 minutes standing may be ignored if the interface is sharply defined.

Transfer in duplicate to dry 18 × 150-mm. test tubes, accurately measured aliquots of the benzene solution, equivalent to 20 micrograms of estradiol. Add a few small pieces of silicon carbide to each tube, and evaporate the solvent on a steam bath without the aid of a current of air, until the ebullition from the silicon carbide just stops. Instantly remove the tubes, wipe them dry quickly, and transfer to an efficient desiccator connected to a vacuum line. Keep the tubes in the desiccator for 1 hour.

To each tube and to a blank tube add a glass bead, and measure into each tube from a burette 1 cc. of the iron-phenol reagent prepared for the test for *Limit of beta-estradiol* under *Estradiol,* page 225, quickly wiping the outside of the burette tip with a piece of absorbent paper before each addition. The burette stopcock must be lubricated only with reagent. The burette should be fitted with a guard tube to exclude moisture and should deliver 1 cc. of the iron-phenol reagent in 30 seconds or less. Immediately close the tubes with rubber finger stalls, and

allow to stand for 30 minutes, shaking the tubes vigorously at 5-minute intervals. Place the tubes in a boiling water bath for 35 minutes, shaking each tube for a few seconds after the first 5 minutes. Transfer to an ice bath for 2 minutes, then remove, and add from a burette exactly 4 cc. of sulfuric acid solution, made by cautiously adding 35 volumes of sulfuric acid to 65 volumes of water. Allow to stand for 5 minutes and mix thoroughly by shaking, first gently, then vigorously. Measure the absorbancies of the solutions of the sample and of the Reference Standard relative to the blank at 525 mμ and at 420 mμ, making any necessary corrections for cell variation.

The quantity, in micrograms, of $C_{18}H_{24}O_2$ in the aliquot used is calculated from the following formula, *A* representing the reading of the absorbancy:

$$20 \times \frac{A\ 525\ \text{m}\mu\ \text{sample} - A\ 420\ \text{m}\mu\ \text{sample}/2}{A\ 525\ \text{m}\mu\ \text{standard} - A\ 420\ \text{m}\mu\ \text{standard}/2}.$$

No lubricants, other than water, shall be used on the stopcocks of the separators in the above assay.

PACKAGING AND STORAGE—Preserve Estradiol Tablets in well-closed containers.

TABLETS AVAILABLE—Estradiol Tablets usually available contain the following amounts of estradiol: 0.1 and 0.2 mg. (1/600 and 1/300 grain).

USUAL DOSE OF ESTRADIOL—0.2 mg. (approximately 1/300 grain).

STATUTORY PROVISIONS INVOLVED

21 U. S. C. 321(g)(2).

"The term 'drug' means * * * (2) articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; * * *"

21 U. S. C. 331.

"The following acts and the causing thereof are hereby prohibited. (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded."

21 U. S. C. 333.

(a) "Any person who violates any of the provisions of section 331, shall be guilty of a misdemeanor and shall on conviction thereof be subject to imprisonment for not more than one year, or a fine of not more than $1,000.00, or both such imprisonment and fine; * * *"

21 U. S. C. 352.

"A drug or device shall be deemed to be misbranded —(a)if its labeling is false or misleading in any particular."

21 U. S. C. 351.

"A drug or device shall be deemed to be misbranded— (c) if it is not subject to the provisions of paragraph (b) of this section and its strength differs from, or its purity or quality falls below that which it purports or is represented to possess."

21 U. S. C. 351.

"(b) If it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls

below, the standards set forth in such compendium. Such determination as to strength, quality or purity shall be made in accordance with the test or methods of assays set forth in such compendium, except that whenever tests or methods of assay have not been prescribed in such compendium or such tests or methods of assay as are prescribed are, in the judgment of the Administrator, insufficient for the making of such determination, the Administrator shall bring such fact to the attention of the appropriate body charged with the revision of such compendium, and if such body fails within a reasonable time to prescribe test or methods or assay which, in the judgment of the Administrator, are sufficient for purposes of this paragraph, then the Administrator shall promulgate regulations prescribing appropriate tests or methods of assay in accordance with which such determination as to strength, quality, or purity shall be made. No drug defined in an official compendium shall be deemed to be adulterated under this paragraph because it differs from the standard of strength, quality, or purity thereof set forth in such compendium, if its difference in strength, quality, or purity from such standard is plainly stated on its label. Whenever the drug is recognized in both the United States Pharmacopoeia and the Homoeopathic Pharmacopoeia of the United States it shall be subject to the requirements of the United States Pharmacopoeia unless it is labeled and offered for sale as a homoeopathic drug, in which case it shall be subject to the provisions of the Homoeopathic Pharmacopoeia of the United States and not to those of the United States Pharmacopoeia."